

SECOND EDITION

# CHEMOTHERAPY *AND* IMMUNOTHERAPY

GUIDELINES AND RECOMMENDATIONS FOR PRACTICE



*Edited by*

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# Contents

|                                                                 |           |                                                               |            |
|-----------------------------------------------------------------|-----------|---------------------------------------------------------------|------------|
| <b>PREFACE.....</b>                                             | <b>IX</b> | C. Chemotherapy classifications.....                          | 68         |
| <b>SECTION I. PROFESSIONAL PRACTICE CONSIDERATIONS .....</b>    | <b>1</b>  | D. Combination chemotherapy principles.....                   | 98         |
| <b>Chapter 1. Professional Practice Considerations .....</b>    | <b>3</b>  | References .....                                              | 98         |
| A. Scope and standards .....                                    | 3         | <b>Chapter 7. Hormone Therapy .....</b>                       | <b>101</b> |
| B. Professional education.....                                  | 3         | A. Hormone therapy in the treatment of cancer .....           | 101        |
| C. Policies and procedures.....                                 | 5         | B. Cancers treated with hormone therapy .....                 | 101        |
| D. Antineoplastic medication safety.....                        | 6         | C. Hormone treatment categories .....                         | 107        |
| E. Quality and safety monitoring.....                           | 9         | References .....                                              | 110        |
| References .....                                                | 9         | <b>Chapter 8. Targeted Therapy .....</b>                      | <b>113</b> |
| <b>Chapter 2. Ethical and Legal Issues.....</b>                 | <b>13</b> | A. Targeted therapies in the treatment of cancer.....         | 113        |
| A. Ethical issues.....                                          | 13        | B. Adverse effects of targeted therapies.....                 | 199        |
| B. Legal issues related to cancer therapy .....                 | 16        | C. Drug–drug interactions .....                               | 199        |
| References .....                                                | 19        | References .....                                              | 199        |
| <b>Chapter 3. Patient Education .....</b>                       | <b>21</b> | <b>Chapter 9. Principles of the Immune System.....</b>        | <b>203</b> |
| A. Patient education overview .....                             | 21        | A. Overview of immunology .....                               | 203        |
| B. Short-term outcomes of patient education .....               | 21        | B. Types of immune response.....                              | 203        |
| C. Long-term outcomes of patient education .....                | 21        | C. Organs of the immune system.....                           | 204        |
| D. Barriers to patient education.....                           | 22        | D. Cells of the immune system.....                            | 205        |
| E. Methods of patient education .....                           | 23        | E. Immune system proteins and receptors.....                  | 206        |
| F. Scope of information.....                                    | 24        | F. Phases of immune response .....                            | 208        |
| G. Documentation.....                                           | 24        | G. Tumor escape mechanisms.....                               | 208        |
| References .....                                                | 25        | References .....                                              | 210        |
| <b>SECTION II. CANCER AND CANCER TREATMENT .....</b>            | <b>27</b> | <b>Chapter 10. Immunotherapy .....</b>                        | <b>213</b> |
| <b>Chapter 4. Overview of Cancer and Cancer Treatment .....</b> | <b>29</b> | A. Overview .....                                             | 213        |
| A. Definition of cancer.....                                    | 29        | B. Modalities of immunotherapy .....                          | 213        |
| B. The Cancer Care Continuum framework.....                     | 31        | C. General patient and family education .....                 | 287        |
| C. Cancer staging and grading .....                             | 33        | References .....                                              | 287        |
| D. Cancer treatment modalities .....                            | 33        | <b>SECTION IV. TREATMENT ADMINISTRATION AND SAFETY.....</b>   | <b>291</b> |
| E. Treatment approaches .....                                   | 37        | <b>Chapter 11. Administration Considerations.....</b>         | <b>293</b> |
| F. Treatment strategies .....                                   | 37        | A. Components of safe and effective administration of         |            |
| G. Measuring response.....                                      | 39        | cancer therapies .....                                        | 293        |
| H. Factors affecting treatment response.....                    | 42        | B. Pretreatment .....                                         | 293        |
| I. Adherence.....                                               | 44        | C. Chemotherapy, targeted therapy, and immunotherapy          |            |
| J. Toxicity grading and documentation.....                      | 48        | dosing .....                                                  | 303        |
| References .....                                                | 49        | D. Verification .....                                         | 306        |
| <b>Chapter 5. Clinical Trials and Drug Development.....</b>     | <b>53</b> | E. Routes of chemotherapy, immunotherapy, and targeted        |            |
| A. Clinical research.....                                       | 53        | therapy administration.....                                   | 308        |
| B. Drug and biologic development process .....                  | 58        | References .....                                              | 334        |
| C. Expanded access .....                                        | 63        | <b>Chapter 12. Safe Handling of Hazardous Drugs .....</b>     | <b>341</b> |
| References .....                                                | 63        | A. Safe handling and disposal of hazardous drugs.....         | 341        |
| <b>SECTION III. CANCER THERAPEUTICS .....</b>                   | <b>65</b> | B. Definition.....                                            | 341        |
| <b>Chapter 6. Chemotherapy .....</b>                            | <b>67</b> | C. Antineoplastic drugs .....                                 | 341        |
| A. Chemotherapy in the treatment of cancer.....                 | 67        | D. NIOSH List of Antineoplastic and Other Hazardous Drugs     |            |
| B. Classification of chemotherapy agents .....                  | 68        | in Healthcare Settings.....                                   | 342        |
|                                                                 |           | E. NIOSH List of Hazardous Drugs in Healthcare Settings ..... | 342        |
|                                                                 |           | F. Immunotherapy .....                                        | 343        |

|                                                                                                |            |                                                                        |            |
|------------------------------------------------------------------------------------------------|------------|------------------------------------------------------------------------|------------|
| G. Routes of occupational exposure.....                                                        | 343        | E. Clinical manifestations.....                                        | 584        |
| H. Hierarchy of hazard controls .....                                                          | 344        | F. Pathologic manifestations associated with drug toxicity.....        | 604        |
| I. Guidelines for personal protective equipment.....                                           | 344        | G. Assessment.....                                                     | 606        |
| J. Storage and labeling.....                                                                   | 345        | H. Collaborative management .....                                      | 608        |
| K. Safe handling precautions during compounding .....                                          | 347        | I. Patient and family education .....                                  | 609        |
| L. Transporting HDs.....                                                                       | 349        | References .....                                                       | 610        |
| M. Safe handling precautions during administration .....                                       | 349        | <b>Chapter 19. Genitourinary Toxicities.....</b>                       | <b>615</b> |
| N. Special precautions for radiopharmaceuticals .....                                          | 350        | A. Overview .....                                                      | 615        |
| O. Handling body fluids.....                                                                   | 350        | B. Antineoplastic-associated genitourinary toxicities.....             | 615        |
| P. Handling patient linens.....                                                                | 351        | C. Drug-specific considerations .....                                  | 636        |
| Q. Disposal of hazardous drugs and materials contaminated<br>with hazardous drugs.....         | 351        | References .....                                                       | 638        |
| R. Procedures following acute hazardous drug exposure.....                                     | 351        | <b>Chapter 20. Altered Sexual and Reproductive Functioning.....</b>    | <b>643</b> |
| S. Spill management.....                                                                       | 352        | A. Alterations in sexual functioning.....                              | 643        |
| T. Requirements for policies regarding the handling of<br>hazardous drugs .....                | 353        | B. Alterations in reproductive functioning.....                        | 650        |
| References .....                                                                               | 354        | References .....                                                       | 653        |
| <b>Chapter 13. Infusion-Related Complications.....</b>                                         | <b>359</b> | <b>Chapter 21. Cutaneous Toxicities and Alopecia .....</b>             | <b>657</b> |
| A. Complications during or shortly after parenteral<br>administration of cancer treatment..... | 359        | A. Cutaneous toxicity .....                                            | 657        |
| B. Extravasation of vesicants resulting in potential<br>tissue damage .....                    | 359        | B. Alopecia .....                                                      | 677        |
| C. Irritation .....                                                                            | 366        | References .....                                                       | 681        |
| D. Flare reaction.....                                                                         | 370        | <b>Chapter 22. Endocrine Toxicities.....</b>                           | <b>685</b> |
| E. Acute infusion-related reactions .....                                                      | 370        | A. Overview .....                                                      | 685        |
| F. Patient and caregiver education .....                                                       | 397        | B. Drug-specific endocrinopathies.....                                 | 685        |
| References .....                                                                               | 397        | C. Immune checkpoint inhibitor-related endocrinopathies .....          | 694        |
| <b>SECTION V. TREATMENT-RELATED COMPLICATIONS .....</b>                                        | <b>403</b> | References .....                                                       | 699        |
| <b>Chapter 14. Myelosuppression.....</b>                                                       | <b>405</b> | <b>Chapter 23. Fatigue .....</b>                                       | <b>703</b> |
| A. Overview .....                                                                              | 405        | A. Overview .....                                                      | 703        |
| B. Types of cytopenias .....                                                                   | 406        | B. Pathophysiology .....                                               | 703        |
| References .....                                                                               | 421        | C. Incidence .....                                                     | 705        |
| <b>Chapter 15. Gastrointestinal and Mucosal Toxicities.....</b>                                | <b>425</b> | D. Assessment.....                                                     | 705        |
| A. Nausea and vomiting .....                                                                   | 425        | E. Collaborative management .....                                      | 706        |
| B. Anorexia and cachexia.....                                                                  | 442        | F. Principles of patient and family education and care planning... 710 |            |
| C. Diarrhea .....                                                                              | 446        | References .....                                                       | 711        |
| D. Colitis.....                                                                                | 457        | <b>Chapter 24. Neurologic Toxicities .....</b>                         | <b>717</b> |
| E. Pancreatitis .....                                                                          | 465        | A. Overview .....                                                      | 717        |
| F. Mucositis.....                                                                              | 467        | B. Radiation-induced central nervous system toxicity .....             | 717        |
| G. Perirectal cellulitis.....                                                                  | 475        | C. Radiation-induced peripheral nervous system toxicity .....          | 725        |
| H. Constipation .....                                                                          | 476        | D. Chemotherapy-induced central nervous system toxicity.....           | 726        |
| References .....                                                                               | 483        | E. Peripheral neuropathy.....                                          | 735        |
| <b>Chapter 16. Cardiovascular Toxicities .....</b>                                             | <b>493</b> | F. Common antineoplastics conferring increased neurotoxicity ... 736   |            |
| A. Overview .....                                                                              | 493        | G. Risk factors and prophylaxis .....                                  | 739        |
| B. Conduction pathway disorders.....                                                           | 493        | H. Cognitive impairment.....                                           | 739        |
| C. Vascular abnormalities .....                                                                | 530        | I. Patient and family education .....                                  | 744        |
| D. Venous thromboembolism.....                                                                 | 532        | References .....                                                       | 746        |
| E. Coronary artery disease .....                                                               | 532        | <b>Chapter 25. Ocular Toxicities.....</b>                              | <b>753</b> |
| F. Left ventricular dysfunction and heart failure.....                                         | 534        | A. Overview .....                                                      | 753        |
| G. Myocarditis.....                                                                            | 537        | B. Pathophysiology .....                                               | 753        |
| References .....                                                                               | 539        | C. Incidence .....                                                     | 757        |
| <b>Chapter 17. Pulmonary Toxicities.....</b>                                                   | <b>543</b> | D. Risk factors .....                                                  | 757        |
| A. Overview .....                                                                              | 543        | E. Clinical manifestations.....                                        | 757        |
| B. Interstitial lung disease.....                                                              | 543        | F. Assessment.....                                                     | 757        |
| C. Diffuse alveolar hemorrhage.....                                                            | 573        | G. Collaborative management .....                                      | 767        |
| D. Acute promyelocytic leukemia treatment-related<br>differentiation syndrome .....            | 574        | H. Patient and family education .....                                  | 767        |
| E. Pleural effusions.....                                                                      | 575        | References .....                                                       | 767        |
| F. Patient and family education .....                                                          | 576        | <b>SECTION VI. POST-TREATMENT .....</b>                                | <b>771</b> |
| References .....                                                                               | 577        | <b>Chapter 26. Post-Treatment and Survivorship Care.....</b>           | <b>773</b> |
| <b>Chapter 18. Hepatic Toxicities.....</b>                                                     | <b>583</b> | A. Overview .....                                                      | 773        |
| A. Overview .....                                                                              | 583        | B. Cancer survivorship care.....                                       | 774        |
| B. Pathophysiology .....                                                                       | 583        | C. Long-term and late effects of cancer treatment.....                 | 775        |
| C. Incidence .....                                                                             | 584        | References .....                                                       | 786        |
| D. Risk factors .....                                                                          | 584        | <b>APPENDICES.....</b>                                                 | <b>791</b> |
|                                                                                                |            | <b>INDEX.....</b>                                                      | <b>803</b> |

# Preface

Oncology nursing is a unique specialty that requires continuous learning to stay up to date on cancer pathophysiology, cutting-edge drugs, and the evidence-based management of cancer and cancer treatment–related toxicities. The Oncology Nursing Society’s (ONS’s) second edition of *Chemotherapy and Immunotherapy Guidelines and Recommendations for Practice* provides nurses with the tools to understand how medications are used in cancer treatment, the effect of medication-related toxicities, and evidence-based recommendations to manage and treat these toxicities. This edition features many new cancer therapies approved since the 2019 publication. Each drug is categorized as chemotherapy, hormone, targeted, or immunotherapy agents. Extensive drug tables in the book provide nurses with tips for managing patients receiving these drugs. The expansion of oral antineoplastic therapies, alone or in combination with infusion therapy, requires that nurses review a patient’s complete cancer treatment plan and consider the side effects, toxicities, and adherence to oral drugs to ensure patient tolerance and efficacy.

This second edition has seen content expanded on the topic of genomics as we move forward in the world of personalized oncology. Health equity is approached with information discussing financial distress, cultural disparities, and health literacy. The latest guidelines and recommendations for treatment, symptom management, and survivorship have been integrated into this new text.

This edition features a QR code, provided with the purchase of this book, to download periodic drug updates. You will see new evidence related to many aspects of cancer nursing care incorporated into this edition, such as hypersensitivity response, safe handling of hazardous drugs, and more.

The editors want to thank all of the contributors who worked tirelessly, despite a pandemic, to make this new edition a reality. This work builds on the knowledge of many generations of oncology nurses and has been used nationally and internationally to guide oncology nursing practice. We are proud to continue to serve oncology nurses worldwide with an essential resource to guide their practice.

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Please scan the QR code to the right to receive periodic updates to select drug tables listed within this book. These updates will help oncology nurses stay up to date with current research and findings related to chemotherapy and immunotherapy guidelines.



## SECTION I

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# Professional Practice Considerations

Chapter 1. Professional Practice Considerations

Chapter 2. Ethical and Legal Issues

Chapter 3. Patient Education



# CHAPTER 1

## Professional Practice Considerations

### A. Scope and standards

1. The safe administration of antineoplastic treatments in various settings is within the oncology nurse's scope of practice (Lubejko & Wilson, 2019).
2. Professional nursing practice is defined and overseen through regulatory influencers and five integral components (American Nurses Association, 2021).
  - a) *Evidence* incorporates scientific and research findings, the expertise of the nurse, and the preferences of the individual.
  - b) *Nursing practice* is the autonomous actions of the professional nurse in any role.
  - c) *Influencers* include state nurse practice acts, the scope and standards that guide practice and specialty practice, and institutional policies and procedures.
  - d) *Safety measures* protect the patient from harm or undesirable outcomes.
  - e) *Quality* strives to obtain desirable outcomes of nursing practice for patients, families, the organization, and the profession.
3. In 2008, the American Society of Clinical Oncology (ASCO) and the Oncology Nursing Society (ONS) began an ongoing collaboration to define and later revise safety standards for chemotherapy and other antineoplastic agents. The *ASCO/ONS Chemotherapy Administration Safety Standards* addressed staffing-related issues, antineoplastic therapy planning, documentation, orders, preparation, patient education, administration, and monitoring for all settings and patient populations (Neuss et al., 2016).

### B. Professional education

1. To promote a safe level of care for individuals receiving chemotherapy, targeted therapy, and immunotherapy, each institution or supporting agency should provide specialized education and preparation consisting of didactic learning followed by successful completion of a clinical practicum (ONS, 2020).
2. Didactic content is comprehensive, current, and evidence based. After the didactic course, a nurse

must demonstrate an understanding of the following (ONS, 2020):

- a) Types of antineoplastic medications, classifications, and routes of administration
  - b) Pharmacology of agents regardless of indications for use
  - c) Pertinent molecular biomarkers, including genomic assays
  - d) Chemotherapy and radiation therapy protectants
  - e) Principles of safe preparation, storage, labeling, transportation, and disposal of agents
  - f) Safe administration procedures
  - g) Procedures for safe handling of hazardous drugs, including spill management
  - h) Appropriate use and disposal of personal protective equipment
  - i) Use of engineering controls, if applicable to the practice setting, including the use of closed-system drug-transfer devices
  - j) Assessment, monitoring, and management of patients receiving therapy
  - k) Medication safety and system safeguards, such as infusion pump safety features
  - l) Appropriate procedures for emergency preparedness, including infusion reactions and extravasation
  - m) Appropriate documentation of treatment administration, patient education, and planned follow-up care and testing
  - n) Patient, family, and caregiver education for these agents, specific to side effects and related symptom management, and the process for urgent and ongoing follow-up
  - o) Education and coordination of post-treatment care and testing, adverse events, and long-term side effects; physical and psychosocial impacts of a cancer diagnosis and treatment; and follow-up care during survivorship
3. Clinical practicum
    - a) The clinical practicum allows the nurse to apply the knowledge gained in the didactic component to direct patient care situations.

- b) Emphasis is placed on the clinical skills that the nurse must demonstrate prior to being deemed competent to administer antineoplastic therapy (see Appendices A and B). The nurse must also display knowledge of organizational policies and procedures related to antineoplastic administration.
  - c) After the clinical practicum, the nurse will be able to perform the following:
    - (1) Demonstrate proficiency regarding safe preparation (when applicable), storage, transport, handling, spill management, administration, and disposal of antineoplastic drugs and equipment.
    - (2) Identify appropriate physical and laboratory assessments for specific agents.
    - (3) Demonstrate skill in venipuncture, including vein selection and maintenance of the site during and after drug administration.
    - (4) Demonstrate skill in the care and use of various vascular access devices.
    - (5) Identify patient and family educational needs related to agents.
    - (6) Identify acute local or systemic reactions, including extravasation and anaphylaxis, associated with antineoplastic drugs and identify appropriate interventions.
    - (7) Demonstrate proficiency in the safe administration of hazardous drugs and disposal of contaminated waste and equipment.
    - (8) Document pertinent information in the medical record.
4. Clinical activities
- a) Pair a nurse new to antineoplastic drug administration with an experienced nurse who can serve as a preceptor and provide clinical supervision and instruction (Lockhart, 2016).
  - b) The preceptor and the nurse establish specific objectives at the beginning of the clinical practicum. Ideally, the nurse and preceptor select a patient assignment. The nurse assumes the responsibility for planning and providing care for this patient under the guidance and supervision of the preceptor.
  - c) The time spent in the clinical practicum is dependent on the nurse's ability to meet specific objectives and institutional requirements.
  - d) The nurse should become proficient and independent in administering nonvesicants before progressing to vesicant administration.
  - e) Various clinical settings can be used for the nurse to demonstrate competency in antineoplastic drug administration. It may not be realistic for all settings or agencies to provide on-site education and training. Alternative methods can be used, including the following:
    - (1) Contracting with larger institutions for didactic education or clinical experience for specific learning needs (e.g., vesicant, nonvesicant, IV push, short infusion, continuous infusion)
    - (2) Creating or using a simulated laboratory to substitute for the clinical component
    - (3) Providing virtual simulation designed to meet specific learning objectives (Konrad et al., 2021)
5. Use an evaluation tool based on the desired outcomes to document the nurse's knowledge of and competency in the following:
- a) Agents and associated nursing implications
  - b) Technical skills required for the administration of agents (e.g., dose calculation, venipuncture, access device management)
  - c) Patient and family education about the treatment regimen
  - d) Steps to take in the event of an untoward response following drug administration (e.g., anaphylaxis, hypersensitivity reaction, extravasation)
6. Competency may be verified in a simulated setting (e.g., skills laboratory) or as a precepted experience in the clinical setting.
- a) The evaluation or documentation tool should meet the needs of the new nurse and the practice setting, including a minimum number of observed and documented antineoplastic drug administrations.
  - b) Observed administration of at least three different agents, types, and routes (i.e., nonvesicant and vesicant; IV push and short-term infusion) is recommended.
  - c) Competency for nontechnical skills, such as patient education, may be verified by role-playing, case scenarios, and observation (Wahl, 2017).
7. Annual continuing education and ongoing competency assessment are required for staff who order, prepare, and administer antineoplastic agents (Neuss et al., 2016).
- a) Educational content should be designed to meet the needs of staff in the healthcare setting (e.g., identified practice problems; high-risk, low volume procedures), and new information should be emphasized (Wahl, 2017).
    - (1) Methods that may be used to identify needs include but are not limited to staff or patient surveys, chart audits, quality improvement studies, clinical observation, and literature review.

- (2) Potential topics include new drugs or drug deliveries, reinforcement or training on policies and procedures, and prevention and management of treatment toxicities.
  - b) Competency assessment is ongoing, may be done by peers or supervisory staff, and is measured in several ways (Lockhart, 2016; Wahl, 2017).
    - (1) Testing
      - (a) Provide a packet of articles for the staff to read or a live educational program followed by an open-book test to measure knowledge.
      - (b) Consider a pretest and post-test to measure individual knowledge gains.
    - (2) Return demonstration
      - (a) Competency checklists can be used to document the performance of technical skills, such as the donning and doffing of personal protective equipment used during drug administration.
      - (b) Staff can also be observed and evaluated using a scoring rubric with a checklist of criteria detailing the steps to take in practice.
      - (c) Examples include monitoring a nurse administering a vesicant or completing dose verification.
      - (d) Actions can be observed in a practice or simulated environment and later debriefed.
    - (3) Simulation
      - (a) Simulation provides a safe environment for staff to practice clinical and critical-thinking skills.
      - (b) Staff can face a clinical challenge and problem-solve the steps to be followed, such as a patient experiencing an infusion reaction or extravasation.
      - (c) Asking nurses, “What would you do if . . .” challenges them to consider the implications of their actions.
      - (d) When a simulation lab is unavailable, it can be performed using role-play and mock scenarios in nearly any location.
  8. Antineoplastic medications administered outside designated oncology areas
    - a) The ONS (2020) position statement on the education of the nurse administering and providing care to patients receiving antineoplastic therapy applies to antineoplastic drugs regardless of indication, route, patient population, or setting.
    - b) All nurses should be knowledgeable about the drugs they administer, including mode of action, side effects, toxicity, dosage range, rate of administration, route of excretion, potential responses, and interactions with other medications and foods.
    - c) The format, length, and specific focus of educational initiatives, both didactic education and clinical experience, may vary according to the needs of the staff and setting. Select staff may require drug- or disease-specific education, whereas others require comprehensive education for all antineoplastic medications.
    - d) The educational plan should be addressed for all individuals working with antineoplastic therapy within institutional policy.
- C. Policies and procedures
1. Policies should be developed using a systematic, evidence-based approach to promote standardization of practice within an institution.
    - a) Policies identify and communicate practice expectations (Dols et al., 2017).
    - b) Procedures are a step-by-step guide to performing a specific task or operation (Esparza, 2019).
  2. Once a policy has been implemented, it must be enforced and followed by staff.
    - a) Individuals can be held liable if patient harm results from failure to follow a policy.
    - b) Institutions can have liability if a policy is unclear, contrasts with another policy, or could be interpreted incorrectly.
  3. Review policies and procedures at least every two years to ensure the practice is current with changing technology and evidence (Esparza, 2019).
  4. Collaboration between departments and professionals is recommended when creating antineoplastic policies and procedures. Input from the pharmacy, medicine, nursing, environmental services, occupational health, and other departments will result in a more comprehensive policy.
  5. Policies related to antineoplastic drug therapy address processes designed to promote the safe and efficient care of patients receiving these medications regardless of setting or department. Topics include the following (Institute for Safe Medication Practices [ISMP], 2022; Neuss et al., 2016):
    - a) Qualifications, including initial educational and ongoing competency requirements, credentialing process, and documentation of staff who order, prepare, and administer antineoplastic therapies
    - b) Hazardous drug management, including safe drug receipt, storage, compounding, transport, use of personal protective equipment, administration, post-treatment care, spill management, disposal, alternative duty, and medical surveil-

lance (Coyne et al., 2019; Polovich & Olsen, 2018; U.S. Pharmacopeial Convention, 2019)

- c) Order writing and dose verification, including process, standard regimens, rounding, cumulative dose, order format, and communication of modifications
- d) Informed consent process
- e) Standardized documentation tools for assessment and care
- f) Toxicity monitoring, including standardized documentation and communication of toxicities
- g) Procedures for care in medical emergencies
- h) Communication of status during transitions of care
- i) Reporting of adverse events and near misses

#### D. Antineoplastic medication safety

1. Published research has found that chemotherapy errors occur in at least 1%–3% of adult and pediatric patients (Reinhardt et al., 2019; Weingart et al., 2018).
  - a) Reinhardt et al. (2019) found a higher incidence of chemotherapy errors (3.6%) for modified or nonstandard orders.
  - b) Other situations identified as a higher risk for error include carboplatin, regimens with three or more agents, and oral chemotherapy (Reinhardt et al., 2019; Weingart et al., 2018).
2. Chemotherapy and other antineoplastic drugs are classified as high-alert medications, regardless of setting, by ISMP (2021). These medications have narrow therapeutic indices (i.e., benefit versus toxicity), multiple potential toxicities, and often are administered in complex regimens, protocols, and schedules (Griffin et al., 2016; Reinhardt et al., 2019; Weingart et al., 2018).
3. Errors may occur at any point during the drug delivery process (Ashokkumar et al., 2018; Reinhardt et al., 2019; Tariq et al., 2021; Weingart et al., 2018).
  - a) Ordering or prescribing errors, including unclear, incomplete, or erroneous orders; drug calculation; dose modification; omission of antineoplastic or supportive drugs or hydration; input and transcription; errors in cycle or day; and cumulative dose documentation or tracking
  - b) Drug preparation errors, including staging or loading a biosafety cabinet with incorrect equipment and supplies, rounding doses, reconstitution, compounding, label application, and dispensing (Gilbert et al., 2018)
  - c) Drug administration errors, including incorrect drug or dose, schedule or timing, patient identification, infusion rate, and route
  - d) Drug monitoring errors, including serum methotrexate level and failure to detect declining left

ventricular function in patients receiving trastuzumab

4. Medication errors can occur after patient discharge from hospital settings.
  - a) Nearly 50% of adult and older adult patients had medication errors or unintentional medication discrepancies after hospital discharge, and 20% reported adverse drug events (Alqenae et al., 2020).
  - b) Supportive medications for chemotherapy and immunotherapy (e.g., leucovorin rescue, anti-diarrheal agents, steroids, antiviral agents) taken incorrectly in the home setting can lead to serious consequences.
  - c) Patient education, clear instructions, and calendars can help prevent errors (Reinhardt et al., 2019).
5. Contributing factors to medication errors (Fyhr et al., 2015; ISMP, 2020; Prakash et al., 2014; Sessions et al., 2019; World Health Organization, 2016)
  - a) Poor communication among healthcare professionals or with patients
  - b) Look-alike, sound-alike medications
  - c) Batching or preparing more than one agent at a time
  - d) Distractions and interruptions
  - e) Heavy workload, fatigue, or stress
  - f) Lack of systematic processes or failure to follow safety processes
  - g) Medication supply and storage issues (e.g., drugs of similar names or dosage strengths stored in close proximity)
  - h) Equipment failure
  - i) Inadequate knowledge or experience of those ordering, preparing, or administering agents
  - j) Patient factors, including literacy, language barriers, and complexity of care
  - k) Ordering errors when using the computer order entry system (e.g., errors due to cut and paste)
6. The following strategies have been used to reduce the risk of medication errors in antineoplastic administration (Billstein-Leber et al., 2018; Coyne et al., 2019; Goldspiel et al., 2015; ISMP, 2022; Kuitunen et al., 2020; Neuss et al., 2016; ONS, 2020).
  - a) Develop policies and procedures using interprofessional collaboration. Include a risk assessment policy and strategies to promote adherence.
  - b) Establish a process of educational preparation and competency of those administering, preparing, or ordering antineoplastic medications. Nurses administering antineoplastic agents are qualified by education and training.
  - c) Ensure current drug information and resources for drug dosing, administration, and side effects are readily available.

- d) Measure and document weight in kilograms and height in centimeters.
- e) Use smart infusion pumps and barcode technology when available.
- f) Follow standards regarding antineoplastic medication orders.
  - (1) Orders are signed manually or by electronic approval by credentialed prescribers (ISMP, 2017a; Neuss et al., 2016).
  - (2) Advanced practice providers (e.g., clinical nurse specialists, nurse practitioners, physician assistants) identify prescribing as one of the most significant parts of their role (Bruinooge et al., 2018). The ability to prescribe antineoplastic medications is determined by the practice location (state and institution) and patient status.
  - (3) Verbal orders for chemotherapy, targeted therapy, and immunotherapy medications are not permitted, except to hold or stop drugs (ISMP, 2017a; Neuss et al., 2016).
  - (4) Text messaging of patient care orders is not permitted (ISMP, 2017b; Joint Commission, 2021).
  - (5) Standardized electronic or preprinted orders should be used for antineoplastic therapies (Neuss et al., 2016).
    - (a) Orders should be regimen based and include the elements outlined by current safety standards.  
Use of standardized, regimen-based preprinted or electronic orders has shown to increase evidence-based oncology care and decrease errors (Coyne et al., 2019; Srinivasamurthy et al., 2021). The National Comprehensive Cancer Network ([www.nccn.org](http://www.nccn.org)) provides disease-specific guidelines and chemotherapy order templates that include suggested patient monitoring for cancer type and stage (e.g., type and timing of imaging) and treatment regimen (e.g., toxicity monitoring). See Appendix C for an example of a chemotherapy order template.
    - (b) Abbreviations, acronyms, and other ambiguous methods of communicating drug information should be avoided.
  - (6) Safety advantages reported with the use of computerized prescriber order entry systems, along with clinical decision support systems, include the removal of interpretation or transcription errors, availability of information about drug doses and schedules, automatic calculation of medication doses, and alert and error-checking functions (Knols et al., 2020; Rahimi et al., 2018; Weingart et al., 2018).
    - (a) Errors in prescribing continue to occur with computerized prescriber order entry, including dose errors, medication choice, incomplete prescriptions, failure to acknowledge electronic alerts, and failure to validate orders.
    - (b) These errors are amplified with new or occasional prescribers and as the complexity of a treatment regimens increases (Weingart et al., 2018).
  - (7) A policy should be in place for prescribing antineoplastic regimens that vary from standard regimens. For example, the prescriber may be required to document supporting references for the variance.
- g) Use safety measures provided in electronic health record systems, such as drug interaction alerts, cumulative dose calculation (when applicable), and override restrictions (Rahimi et al., 2018; Reinhardt et al., 2019). In a study examining chemotherapy errors and electronic prescribing, Reinhardt et al. (2019) found that 61% could be avoided through further software development.
- h) Require at least two approved practitioners to perform dose and drug verification for all routes of delivery before preparation, upon preparation, and prior to administering antineoplastic medications (Neuss et al., 2016).
  - (1) Independent dual verification (i.e., independent double checks) is a process in which a second person verifies the accuracy of a prescribed therapy without revealing their findings to the other verifier until both have completed the process (ISMP, 2019).
  - (2) Numerous studies have demonstrated the ability of independent double checks to detect up to 95% of errors (Alsulami et al., 2012; ISMP, 2019).
  - (3) Identifying areas of vulnerability, training staff, and using checklists promotes an effective and consistent process (ISMP, 2019; Macias et al., 2018; Schwappach et al., 2018; see Appendix D).
  - (4) Prior to administering antineoplastic agents, the treatment plan should be reviewed. Orders, medication, patient identification, and pump programming must also be verified (Neuss et al., 2016).



See Chapter 11 for more information on dose verification.

- (5) Conducting a comprehensive review of the medication orders, including comparing the previous cycle rather than comparing the product to the order, is invaluable in catching prescribing errors (ISMP, 2019; Reinhardt et al., 2019).
- (6) Drug and dose verification must be performed in a distraction-free setting. Using timeout and speaking-out-loud checks at drug administration has increased safety (Coyne et al., 2019; Kalo et al., 2019; Prakash et al., 2014).
- (7) Creative staffing models can minimize interruptions with dose verification (Baldwin & Rodriguez, 2016).
- (8) Practitioner dose verification combined with automated double checks (e.g., barcode scanning) may improve safety (ISMP, 2019; Macias et al., 2018).
- i) Procedures for emergency preparedness should be established.
  - (1) 24–7 triage should be provided (e.g., on-call practitioners, emergency departments) (Neuss et al., 2016).
  - (2) At least one clinical staff member certified in basic life support must be present during chemotherapy administration. Staff certified in advanced cardiac life support or pediatric advanced life support may be indicated depending on the setting and treatment delivered (Neuss et al., 2016).
  - (3) When antineoplastics are administered in the healthcare setting, a licensed independent practitioner must be on site and immediately available to staff (Centers for Medicare and Medicaid Services, 2020; Neuss et al., 2016).
  - (4) Policies, procedures, and standardized orders should be in place to manage medical emergencies (ISMP, 2022; Neuss et al., 2016; Shaker et al., 2020). Procedures include the process for monitoring and tracking the availability and readiness of emergency equipment and the expiration date on medications, including antidotes and rescue agents.
  - (5) Staff should be educated regarding who to call and the process for contacting the provider or healthcare team (e.g., outpatient nurses need to be clear as to whether to contact 911 or the institution's code team).
  - (6) Orders for the treatment of infusion emergencies should be available to enable immediate intervention without waiting for the provider's order, with indications for each medication clearly defined (e.g., epinephrine, diphenhydramine, steroids) (Shaker et al., 2020).
- (7) All team members should understand their role and responsibilities in an emergency.
- (8) Verify that emergency equipment and supplies, including oxygen, are available and working and that staff are aware of their location. Infusion chairs functional to change position are recommended if needed.
- (9) Policies, procedures, and standardized orders should be established, with antidotes in place to manage vesicant extravasation (Neuss et al., 2016; see Chapter 13).
  - (a) Staff must be knowledgeable regarding the management of extravasation, the location of orders, and the process for obtaining antidotes.
  - (b) Coupled order sets, such as the inclusion of an order on the antineoplastic therapy order set (e.g., initiate extravasation orders for suspected extravasation), permit the prompt and evidence-based management of emergencies such as extravasation (ISMP, 2010).
- (10) Antidotes or rescue agents (where applicable) with directions for use should be readily available.
- (11) Process improvement projects and educational programs should be designed to provide patients with prompt, evidence-based interventions.
  - (a) Evaluate previous emergent situations to determine what worked and areas for improvement.
  - (b) Consider running mock codes and infusion reaction drills. Numerous studies have shown that these drills increase practitioner proficiency and confidence and decrease anxiety (Josey et al., 2018; LeBoeuf & Pritchett, 2020; Sharour, 2019).
- j) Standardized processes should be designed to promote effective communication and handoffs between care providers and care sites for patients receiving antineoplastic therapy (Coyne et al., 2019; Neuss et al., 2016).
  - (1) The highest safety risk times during drug administration should be identified to allow for clear communication.

- (2) Safety is improved with open interprofessional communication and a clear understanding of roles, responsibilities, accountability, and a process to de-escalate problems.
  - (3) Nursing bedside rounds and interprofessional rounds have been found to increase communication and decrease errors (Daniels, 2016).
  - (4) Any missed patient appointments or treatments should be documented, and follow-up should occur with the patient and other healthcare team members.
  - (5) An accurate treatment summary must be documented, including history, previous cancer treatments, and current treatment when a patient is transferred to a different healthcare setting. The ASCO Institute for Quality provides example templates on its website ([www.instituteforquality.org/cancer-treatment-plan-and-summary-templates](http://www.instituteforquality.org/cancer-treatment-plan-and-summary-templates)).
  - k) Ongoing patient education should be provided, including information, motivation, and encouragement to patients to become vigilant partners in safety measures (Coyne et al., 2019; Weingart et al., 2018).
7. Drug shortages in oncology care are multifactorial. Driving forces include low profitability for manufacturers of generic drugs, decreased drug quality in production, mergers of manufacturers, complex supply chains, natural disasters, and regulatory challenges (Jacob, 2020).
- a) Drug shortages can have significant clinical effects (Alpert & Jacobson, 2019; ISMP, 2018b; Unguru, 2020; U.S. Food and Drug Administration [FDA], n.d.).
    - (1) Treatment outcomes can be affected by omitted or reduced doses from delays or changes in treatment regimens.
    - (2) Medication errors
      - (a) Healthcare providers may not know about substitute medications when the preferred drug is unavailable, potentially resulting in errors in dosing, adverse effects, and drug interactions.
      - (b) A different concentration or brand is purchased, potentially affecting how the dose is prepared, dispensed, and administered.
      - (c) Look-alike or sound-alike medications are purchased from a different manufacturer.
    - (3) Increased costs
      - (a) Cost of replacement medications may be significant.
      - (b) Labor costs are associated with seeking replacement supplies, managing inventory, updating computer systems for replacement medications, and educating staff. These costs are estimated at \$359 million per year (Kacik, 2019).
      - (c) Financial and emotional burdens placed on patients can negatively affect patient satisfaction.
    - b) The Food and Drug Administration Safety and Innovation Act of 2012 requires pharmaceutical companies to notify FDA when a product may be affected by production changes or manufacturing interruptions (U.S. FDA, 2018).
    - c) FDA (n.d.) works with manufacturers to minimize the impact of drug shortages. A list of drugs in short supply is maintained on the FDA website ([www.accessdata.fda.gov/scripts/drugshortages/default.cfm](http://www.accessdata.fda.gov/scripts/drugshortages/default.cfm)).
- E. Quality and safety monitoring and improvement programs are encouraged in each practice setting (Neuss et al., 2016).
1. Third-party assessments in oncology related to the delivery of antineoplastic medications include the following organizations:
    - a) American College of Surgeons Commission on Cancer (ACoS CoC)
    - b) ASCO Quality Oncology Practice Initiative Certification Program (QOPI)
    - c) Foundation for the Accreditation of Cellular Therapy (FACT)
  2. Quality monitoring is encouraged in each setting, using internal and external data to establish benchmarks (ISMP, 2022). Topics for monitoring should meet the needs of the practice setting. Examples include the following:
    - a) Oral oncolytic management, including adherence, education, and prescribing processes
    - b) Care coordination, including communication at the transition of care
    - c) Access device management, including with infections and occlusions
    - d) Drug administration, including medication errors, safe handling of hazardous drugs, extravasation, and infusion reactions

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## CHAPTER 2

# Ethical and Legal Issues

### A. Ethical issues

1. The ever-changing healthcare environment necessitates sensitivity to ethical and legal issues. Concerns arise in the care of all patients. However, they often have heightened intensity and complexity in the cancer population, as patients, families, and healthcare professionals face frequent and potentially difficult moral choices.
2. *Ethics* is a term that describes what is expected as correct and principled behavior. Issues may arise when conflicting values exist among individuals, groups, or organizations (Beauchamp & Childress, 2019).
3. Ethical issues related to cancer therapy
  - a) Healthcare realities that present potential ethical issues include the following:
    - (1) Major advances with increased availability and access to medical technology, heightened expectations, and changing moral attitudes combine to generate complex ethical and legal problems related to cancer and palliative care (Bressler et al., 2017; Butts & Rich, 2020). In particular, the use of life-sustaining measures may raise ethical questions when healthcare professionals perform the following errors (Kates, 2017; Marcelin et al., 2019; Sirilla et al., 2017; Sisk et al., 2016; Sullivan & Dickerson, 2016):
      - (a) Fail to discuss patient requests before a crisis develops
      - (b) Are reluctant or fail to communicate medical treatment options with a stressed and grief-stricken family
      - (c) Fail to consider supportive care measures
      - (d) Experience moral distress related to personal values or biases
    - (2) The changing healthcare environment (e.g., staffing shortages, reallocation of resources, consolidation, corporatization) has resulted in growing administrative dominance over clinical practice (Agency

for Healthcare Research and Quality, 2019; Figueroa et al., 2019).

- b) The large number of underinsured and undocumented individuals has led to ethical dilemmas in health care.
  - (1) Even for people with health insurance, co-payments or deductibles can lead to substantial debt (Yousuf Zafar, 2016).
  - (2) Financial toxicity is the unintended and unanticipated financial burden experienced by patients and is associated with negative consequences and increased risk of mortality (Witte et al., 2019). This definition includes a range of concerns from minimal financial vulnerability and worry to extreme financial toxicity.
    - (a) The adverse impact of a cancer diagnosis on financial well-being may result from direct or indirect costs and can be both objective and subjective (Arastu et al., 2020; Coumoundouros et al., 2019; Edward, 2020; Singleterry, 2017).
      - i. Material loss, including savings, home, loss of insurance, bankruptcy
      - ii. Balancing cancer care costs with family, food, housing, child care, and transportation
      - iii. Psychological distress related to uncertainty and resource insecurity
      - iv. Maladaptive coping strategies
      - v. Sense of loss of control
      - vi. Sense of vulnerability
    - (b) Consequences of financial toxicity may be immediate or long term.
      - i. Treatment nonadherence
      - ii. Decreased health-related quality of life
      - iii. Bankruptcy

- iv. Increased risk of mortality
- v. Changing family dynamics
- c) Informal caregivers are the primary source of support for patients with cancer, assisting with household tasks, medical care, and emotional support (Counmoundouros et al., 2019).
  - (1) Responsibilities often result in high levels of emotional, physical, social, and financial burden for the caregiver.
  - (2) The demand for informal cancer caregivers will increase as life expectancy rises and cancer incidence increases.
  - (3) Care time is the greatest source of caregiver cost and stress. Other sources include out-of-pocket and absenteeism costs.
- d) Some groups are at higher risk for perceived subjective financial distress resulting from objective financial burden.
  - (1) Individuals with lower socioeconomic status and multiple comorbidities may struggle to pay for daily living needs, such as food, housing, and monthly bills (Zheng et al., 2020).
  - (2) Children, younger cancer survivors, and low-income families are most affected by limited coverage and higher deductibles. Payment for care must be addressed for protected groups, such as incarcerated and homeless individuals (Lyckholm & Glancey, 2016; Yousuf Zafar, 2016).
  - (3) Some insurance plans do not cover select diagnostic testing or more expensive treatments, such as hematopoietic stem cell transplantation, proton beam therapy, clinical trials, or off-label use of medications (Brown et al., 2016; Centers for Medicare and Medicaid Services, 2022).
  - (4) Theoretical frameworks that incorporate medical and nonmedical aspects of financial hardship are limited, making it challenging to fully understand the interrelationship between cancer survivors and those with no personal history of cancer.
- e) Strategies to anticipate and reduce financial concerns along the cancer trajectory include the following:
  - (1) Increased transparency concerning costs of office visits, diagnostics, treatment, and palliative and other supportive care
  - (2) Early discussion of payment options and financial assistance
  - (3) Follow-up on financial discussions as circumstances change
  - (4) Practical suggestions for keeping track of precertifications, bills, and payments
  - (5) Clear discussion of goals, benefits, and costs of care
  - (6) Early referral to supportive services and navigation
  - (7) Access to a National Cancer Institute comprehensive cancer center
- f) Improvement requires multilevel, coordinated efforts among stakeholders, including patients, providers, health systems, payers, manufacturers, and policymakers (Edward, 2020; Lentz et al., 2019).
  - (1) Monitor the financial status of patient groups and their perceptions of subjective financial distress at different times (e.g., diagnosis, curative or palliative treatment, survivorship care).
  - (2) Evaluate the healthcare process by measuring changes in financial status in individual patients and groups.
  - (3) Assess the seriousness of the financial situation at different time frames.
  - (4) Individualize information and counseling needs.
- g) Expanding awareness and appreciation of cultural diversity is essential (Bressler et al., 2017).
  - (1) Cultural disparities in cancer care are unfavorable health outcomes related to inequities in health insurance coverage, access to and use of care, and quality of care (Pirschel, 2020; Underwood, 2019).
    - (a) Disparities adversely affect groups that have systematically experienced greater obstacles to health based on race or ethnicity; language and communication skills; religion; socioeconomic status; gender; age; mental health; cognitive, sensory, or physical disability; sexual orientation or gender identity; geographic location; or other characteristics historically linked to discrimination or exclusion (Office of Disease Prevention and Health Promotion, n.d.).
    - (b) A society is considered to have cultural diversity if it has many different cultural or ethnic groups. This includes social status, culture, language and communication skills, religion, personality, race and ethnicity, age, gender, sexual orientation, and decision-making ability (Betancur et al., 2020; Underwood, 2019).
    - (c) Social determinants of health are the conditions in an environment that impact an individual's health, func-

- tioning, and quality of life (Office of Disease Prevention and Health Promotion, n.d.). The five domains are economic stability, education, health care, neighborhood, and community context.
- (d) Cultural and communication differences and protections present challenges from discussion of surveillance, diagnosis, and prognosis to decisions about who will provide long-term care (Agency for Healthcare Research and Quality, 2019; Bressler et al., 2017; Butts & Rich, 2020).
  - (e) Implicit bias describes attitudes toward or associated stereotypes with individuals or groups of people without conscious knowledge.
  - (f) Designated priority populations are the focus of federal efforts to reduce disparities and include people of color, low-income populations, women, children or adolescents, older adults, individuals with special healthcare needs, and individuals living in rural and inner-city areas (Agrawal & Enekeuchi, 2020).
- (2) Actions to improve cultural awareness (Marcelin et al., 2019; Pirschel, 2020)
- (a) Begin the conversation during assessment and continue throughout the trajectory.
  - (b) Recognize personal biases.
  - (c) Identify individuals at risk for developing preventable cancer.
  - (d) Allow a safe space for a conversation about concerns.
  - (e) Provide education about cultures.
  - (f) Provide translation services.
  - (g) Personalize surveillance and management for cancer.
  - (h) Respect cultural differences.
  - (i) Display patient nondiscrimination policy and patient bill of rights.
  - (j) Encourage neutral language, asking for preferences.
  - (k) Be honest.
  - (l) Follow the tenets of the American Nurses Association (2015) code of ethics.
- (3) Advocacy for patients of diverse backgrounds
- (a) Coordinate community efforts to promote awareness of implicit and explicit bias, prejudice, and discrimination.
  - (b) Apply efforts to counteract implicit and explicit bias, prejudice, and discrimination.
  - (c) Address root causes of disparities in cancer care, including insurance issues and access to care.
  - (d) Use alternative therapies.
    - i. Evidence-based complementary and alternative medicine, in conjunction with or as a substitute for conventional treatment, is affected by variations in individual response to cancer and its treatment, the need for a sense of control, belief in individual rights and determination, and cultural and spiritual beliefs. Caregiver beliefs often limit the use of such therapies.
    - ii. In the search for cancer care with minimal side effects, survivors and families often embark on unproven therapies, which can cause adverse outcomes and insurmountable costs (Johnson et al., 2017).
    - iii. Oncology nurses must be educated about alternative methods to provide education about reliable options (American College of Surgeons Commission on Cancer, 2021; Butts & Rich, 2020; Cox et al., 2017).
  - (e) Precision oncology: As biomarker testing that leads to the use of targeted therapies becomes the standard of care, healthcare professionals are expected to apply this expanding science to practice and be aware of biomarker-directed targeted therapies and their mechanism of action, indications, and symptom management.
    - i. Understanding the technology and options for biomarker testing and its impact on care requires ongoing education.
    - ii. Reimbursement for testing and services, collection of an extensive family history, and costs of targeted and biologic therapies offer addi-

- tional challenges to patients, healthcare systems, and professionals (American Nurses Association & International Society of Nurses in Genetics, 2016; Mohammed et al., 2016; Roeland et al., 2017).
4. Ethical issues that oncology nurses face in daily practice (de Groot et al., 2017; Fiore & Goodman, 2016; Sisk et al., 2016; Sullivan & Dickerson, 2016)
    - a) Autonomy
      - (1) Patient autonomy and decision-making capacity
      - (2) Informed consent
      - (3) Cancer risk reduction (e.g., prophylactic surgeries)
      - (4) Treatment during pregnancy
      - (5) The right to refuse treatment
      - (6) Disparities in the wishes of a patient and their significant other
      - (7) Advocating for individuals who exhibit risky behaviors or make choices with which the caregiver disagrees
      - (8) Privacy in communications (e.g., medical records, messaging, telemedicine)
    - b) Healthcare environment and reform
      - (1) Undertreatment of pain, particularly in light of the opioid crisis
      - (2) Inequities in cancer care
      - (3) Access to care and clinical trials
      - (4) Access to high-cost cancer drugs and drug shortages
      - (5) Cultural diversity and potential bias
      - (6) Balance and justice in cancer care
      - (7) Expanding the use of telehealth
    - c) End-of-life and prolongation-of-life decisions
      - (1) Assisted dying (legal in several states)
      - (2) Treatment futility versus continuing experimental treatment
      - (3) Prognosis-related discussions
    - d) Confidentiality
      - (1) Biomarker testing and disclosure of results
      - (2) Scientific integrity
      - (3) Big data collection and warehousing
    - e) Conflict resolution and critical conversations
      - (1) Intrafamily conflicts
      - (2) Nurse–family conflicts
      - (3) Nurse–physician conflicts
      - (4) Physician–family conflicts
      - (5) Clarity in communications
    - f) Professional boundaries
      - (1) Giving or receiving gifts
      - (2) Social media (e.g., friend requests from patients)
      - (3) Electronic messaging
  5. The Joint Commission (2020) requires accredited institutions to provide access to an ethics consultation to assist in evaluating the decision-making capacity of an individual and assist with problem resolution.
  6. The ethical principles guiding decision-making are summarized in Table 2-1.
  7. The American Nurses Association (2015) code of ethics serves as an ethical framework for practice, providing direction regarding ethical relationships, nursing responsibilities, appropriate behaviors, and decision-making. Components of the framework include the following:
    - a) Respect for the inherent dignity, worth, and unique attributes of every person
    - b) Primary commitment to the patient
    - c) Protection of the rights, health, and safety of the patient
    - d) Authority, accountability, and responsibility for nursing practice
    - e) Same duties owed to self as to others
    - f) Establishment, maintenance, and improvement of the ethical environment of the work setting and conditions of employment
    - g) Advancement of the profession through research and scholarly inquiry
    - h) Protection of human rights, promotion of health diplomacy, and reduction of health disparities
    - i) Articulation of nursing values, maintenance of the integrity of the profession, and integration of the principle of social justice
- B. Legal issues related to cancer therapy
1. Adhering to national, state, and institutional standards is a fundamental responsibility of all nurses (American Nurses Association, 2015; Brown et al., 2016; Centers for Medicare and Medicaid Services, 2022).
  2. Acts and standards guiding oncology nursing practice are not all-inclusive, as the changing environment requires knowledge of specialty competencies depending on the practice setting.
    - a) Nurse practice acts are state laws that define nursing performance in fundamental terms for each state (American Nurses Association, 2021).
    - b) The Oncology Nursing Society's *Scope and Standards of Oncology Nursing Practice* explains the minimum standard of care by which an oncology nurse is expected to practice (Lubejko & Wilson, 2019).
    - c) The *American Society of Clinical Oncology/Oncology Nursing Society Chemotherapy Administration Safety Standards* detail the safety standards for chemotherapy prescription, preparation,

**TABLE 2-1.** Ethical Principles

| Principle      | Description                                                                    | Clinical Examples                                                                                                                                                                                 |
|----------------|--------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Autonomy       | Independent decision-making by an individual following their own best interest | Respecting an individual's choice, even when different from one's own<br>Providing supportive services                                                                                            |
| Beneficence    | The duty to act in the best interest of the involved person                    | Personalizing care based on individual desires, culture, disease, and other factors<br>Providing evidence-based care                                                                              |
| Fidelity       | Faithfulness to promises made                                                  | Providing follow-up as promised<br>Providing survivorship care planning<br>Fostering collegiality                                                                                                 |
| Justice        | Equitable distribution of available resources                                  | Offering or providing treatment regardless of ability to pay, culture, or socioeconomic status<br>Assisting with or referring for financial support                                               |
| Nonmaleficence | The duty to do no harm                                                         | Providing complete information<br>Providing survivorship services<br>Recognizing professional limitations and seeking consultation or collaboration<br>Adhering to professional standards of care |
| Veracity       | Truth telling                                                                  | Explaining treatment in understandable terms before it is initiated<br>Providing accurate information and educational materials                                                                   |

Note. Based on information from Beauchamp & Childress, 2019.

administration, and monitoring in all practice settings (Neuss et al., 2016).

- d) *Genetics/Genomics Nursing: Scope and Standards of Practice* describes standards and scope of practice for general and advanced practice nurses addressing genetic and genomic issues with examples from various practice settings (American Nurses Association & International Society of Nurses in Genetics, 2016).
- e) The Oncology Nursing Society's *Access Device Standards of Practice for Oncology Nursing* details the current standards for using access devices in cancer care (Camp-Sorrell & Matey, 2017).
- f) *Infusion Therapy Standards of Practice* explain the current standards of nursing practice for IV therapy (Infusion Nurses Society, 2021).
- g) American College of Surgeons Commission on Cancer's (2022) *Optimal Resources for Cancer Care* encompasses the requirements that cancer programs must meet to earn and maintain Commission on Cancer accreditation.
- h) Institution-specific standards may be outlined in the following:
  - (1) Standards of practice
  - (2) Nursing policy and procedure manuals
  - (3) Job descriptions
  - (4) Institutional review board decisions and guidance

### 3. Common legal issues

- a) Medication errors (see Chapter 1)
- b) Documentation issues: The duty to keep accurate records is a fundamental nursing responsibility. The medical record is scrutinized in the event of litigious action and is believed to reflect the care rendered (Naidu & Alicia, 2019; Neuss et al., 2016).
  - (1) Common documentation errors
    - (a) Omitting significant observations
    - (b) Failing to document response to an intervention
    - (c) Failing to document patient teaching and understanding
    - (d) Failing to document what was taught and to whom
  - (2) Nursing actions to include in the documentation
    - (a) Telephone, text, or other digital communications or conversations, particularly those in which nurses give patients instructions or advice
    - (b) Fax and email communications, particularly those in which the nurses give patients instructions or advice
    - (c) Virtual face-to-face communications, particularly those in which nurses give patients instructions or advice,



- including the type of communication, who was included, and the location (e.g., online meetings, forums, email distribution lists, telemedicine) (Knudsen et al., 2021)
  - (d) Pertinent conversations with patients, families, or other caregivers
  - (e) Interagency referrals, including telephone conversations with providers
  - (f) Antineoplastic drug administration (see Appendices A and B)
  - (g) Treatment-related documentation
    - i. Completion of independent verification of drug and dose
    - ii. Two unique patient identifiers (e.g., name, medical record number, date of birth)
    - iii. Patient-specific measurements used to calculate doses (e.g., body surface area)
    - iv. Pertinent laboratory and diagnostic test results
    - v. Date and time of therapy
    - vi. Drug name, dose, route, location of administration, and infusion duration
    - vii. Volume and type of IV fluids administered
    - viii. Assessment of the IV site before, during, and after infusion
    - ix. Information about the infusion device (e.g., vein selection, needle size, type of device, infusion pump)
    - x. Verification of venous access device patency, including the presence of a blood return before, during, and after IV therapy (also any issues with venous access)
  - (h) Patient assessment and evaluation of patient response to and tolerance of treatment
  - (i) Patient and family education related to the drugs received, toxicities, toxicity management, and follow-up care (especially when and who to call with specific resource numbers and times)
  - (j) Post-treatment or discharge instructions
- c) Informed consent
- (1) Process
    - (a) Patients must give informed consent for treatment, enrollment in a clinical trial, or participation in nursing research (Beauchamp & Childress, 2019; Butts & Rich, 2020; Klimaszewski, 2016).
    - (b) Except for research, each institution determines its practice related to how and if a patient must provide written informed consent before receiving cancer treatment, such as antineoplastic agents, targeted therapies, or immunotherapies (Neuss et al., 2016).
    - (c) It is essential to maintain consistency between policy and practice throughout the institution.
    - (d) Regardless of the method used to document informed consent, all needed elements of the informed decision-making process must be included. The following approaches have been used:
      - i. The patient signs a designated antineoplastic therapy consent form explicitly designed for administering chemotherapy, targeted therapy, or immunotherapy. This document reflects patient education, remains part of the medical record, and might be preferred by risk management. A sample template for chemotherapy consent is provided in Appendix E.
      - ii. The general hospital consent to treat serves as the signed permission to provide antineoplastic medications.
      - iii. Some centers use a general procedure consent form for cancer treatment.
      - iv. A specific form is not signed, but consent is documented within the medical record.
  - (2) Elements of consent (Elements of Informed Consent, 2022)
    - (a) Disclosure: The patient is informed of their cancer diagnosis, including the type, location, and stage.
    - (b) The patient is informed of the prognosis and goal of the proposed treatment (e.g., cure, control, palliation).
    - (c) Possible benefits of the treatment are discussed.
    - (d) Possible risks and adverse effects are discussed, including short- and long-term side effects.

- (e) Alternatives to treatment and associated risks are covered. Palliative care should be offered as an option when appropriate.
- (f) Patients younger than age 18 years may be legally able to give informed consent if they are emancipated minors. Assent is the willingness to participate in treatment by people who are, by definition, too young to give informed consent but are old enough to understand the diagnosis and proposed treatment (Neuss et al., 2016).
  - i. If assent is given, informed consent must still be obtained from the patient's parents or guardian.
  - ii. The main goal of child assent is to protect children involved in clinical trials (Tait & Geisser, 2017).
- (3) Requirements
  - (a) The informed consent document must state the right of the patient to refuse or discontinue treatment at any time.
  - (b) The informed consent document and, subsequently, healthcare providers assure patients that ongoing support and care will be provided if they decline or discontinue treatment connected with the trial or research.
  - (c) Nurses and physicians have different but complementary roles in the informed consent process.
  - (d) See Chapter 5 for additional information on the informed consent process related to clinical trials and the nurse's role.

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## CHAPTER 3

# Patient Education

### A. Patient education overview

1. Patient education includes learning experiences that empower individuals or communities with health information. This is combined with instructions to help patients understand how to care for themselves throughout the treatment trajectory, when to obtain help in their care, and the risks of illness and how to prevent it.
2. Patient education is a continuous process throughout the cancer journey (Gidron, 2016; Vaartio-Rajalin et al., 2015).
  - a) Health education and promotion are key roles of the nursing profession, especially for oncology nurses. Education is essential for patients, their significant others, and the public.
    - (1) Using the models of patient engagement and shared decision-making, all practitioners must be involved in health education and promotion.
    - (2) This requires open collaboration and interprofessional communication across all healthcare settings (American Nurses Association, 2015; Blecher et al., 2016; Brant & Wickham, 2013; Tariman et al., 2016; Vaartio-Rajalin et al., 2015).
  - b) The Agency for Healthcare Research and Quality (AHRQ, 2020a) has identified universal precautions for health literacy; steps aimed at improving the communication of healthcare information, leading to improved comprehension and access; improving patients' ability to navigate the healthcare system; and supporting patients in their self-care.
  - c) Health literacy can be divided into personal or organizational health.
    - (1) *Personal health literacy* is defined by the Office of Disease Prevention and Health Promotion (2021) as “the degree to which individuals have the ability to find, understand, and use information and services to make informed health-related decisions and actions for themselves and others” (para. 3).

- (2) *Organizational health literacy* is defined by the Office of Disease Prevention and Health Promotion (2021) as “the degree to which organizations equitably enable individuals to find, understand, and use information and services to inform health-related decisions and actions for themselves and others” (para. 3).
- (3) According to the *National Action Plan to Improve Health Literacy*, “nearly 9 out of 10 adults have difficulty using the everyday health information that is routinely available in our health care facilities, retail outlets, media, and communities” (Office of Disease Prevention and Health Promotion, 2010, p. 6).
- (4) Given the high prevalence of low health literacy, the application of health literacy best practices should be universally applied to all patients. To support these efforts, AHRQ created the universal precautions approach to patient education (AHRQ, 2020).

### B. Short-term outcomes of patient education (Blecher et al., 2016; Neuss et al., 2016)

1. Empowerment of active participation in care
2. Autonomous decision-making regarding treatment options or the right to refuse treatment
3. An understanding of diagnosis and treatment options
4. Ability to communicate an understanding of the goals and duration of treatment
5. Identification of short- and long-term side effects, including those that need to be reported
6. Demonstration of the ability to perform self-care or adapt to potential limitations
7. Promotion of adaptive skills in a life-threatening situation
8. Identification and use of community resources

### C. Long-term outcomes of patient education (Joint Commission, 2021)

1. Improvement in self-care behaviors
2. Improvement in health-related quality of life
3. Decreased healthcare costs
4. Increased customer satisfaction
5. Improved ability to make informed healthcare decisions

#### D. Barriers to patient education

1. Barriers should be assessed on an individual basis. A learning needs assessment should be performed and documented to identify obstacles that prevent the effective delivery of healthcare information (Gumusay et al., 2016; Joint Commission, 2021; Neuss et al., 2016).
2. Barriers to learning
  - a) The individual's cognitive resources, including potential for problems with attention, working memory, or information processing related to the disease or treatment (Jewitt et al., 2016; Vaartio-Rajalin et al., 2015)
  - b) Lack of knowledge or understanding of the diagnosis and treatment plan and differences in professional and patient knowledge expectations (Jewitt et al., 2016; Vaartio-Rajalin et al., 2015)
  - c) Differing expectations of the purpose of treatment between the patient, caregiver, and healthcare team
  - d) Concerns or misconceptions regarding therapy due to prior experience or the experience of a friend or relative, which may deter the patient from undergoing treatment
  - e) Language barriers
    - (1) Access to effective interpreter translation services in real time can be a barrier.
    - (2) The 2020 U.S. Census concluded that 21.5% of residents speak a language other than English in the home (U.S. Census Bureau, n.d.).
    - (3) Language barriers keep patients from engaging in seamless conversations with their doctors and interacting with the healthcare industry.
  - f) Educational barriers
    - (1) The national adjusted cohort graduation rate for public high school students in 2018–2019 was 86%. This represents the highest rate since its first measurement in 2010–2011. Asian/Pacific Islander students had the highest rate (93%), followed by White (89%), Hispanic (82%), Black (80%), and American Indian/Alaska Native (74%) students (National Center for Education Statistics, 2021).
    - (2) High school graduation rates were historically low before 1950, putting older indi-

viduals at an increased risk for educational barriers (Swanson, 2010).

- g) Effects of low health literacy (AHRQ, 2020b; Centers for Disease Control and Prevention, 2015, 2021; Joint Commission, 2021; Katz, 2017; Nielsen-Bohlman et al., 2004)
  - (1) Poor patient outcomes
  - (2) Increased healthcare costs
  - (3) Increased risk for medication errors
  - (4) Inability to follow treatment instructions
  - (5) Less success navigating the healthcare system
  - (6) Increased risk for hospitalization
- h) Physical barriers, such as pain, visual disturbances, auditory or cognitive impairments, and the inability to speak, can interfere with comprehension (Joint Commission, 2021).
- i) Access is reduced because of geographic barriers, such as the availability of transportation and the distance from home to the treatment facility.
- j) Psychosocial or emotional issues may create barriers to learning and need to be addressed before learning occurs (Joint Commission, 2021).
- k) Interprofessional care coordination and communication barriers (Joint Commission, 2021; Tariman et al., 2016; Vaartio-Rajalin et al., 2015)
  - (1) Ineffective communication among healthcare team members
  - (2) Ineffective communication among healthcare facilities
  - (3) Differences among healthcare professionals in their perceptions of the patient education process
- l) Methods of overcoming barriers
  - (1) Facilitate time for patients to express concerns and attempt to manage their anxiety.
  - (2) Assess cognitive resources and knowledge expectations of the individuals being educated, keeping in mind that educational level alone does not always give the complete picture of an individual's abilities.
  - (3) Include the patient's support system (e.g., family, friends, significant others) in the patient education process, providing support to the patient and help with learning.
  - (4) Manage physical barriers, such as pain, and ensure that learners have all necessary assistive devices (e.g., glasses, hearing aids).
  - (5) Provide access to an interpreter, either in person or through telecommunication (Joint Commission, 2021).
    - (a) Hospitals are required to ensure the competency of interpreters and translators.



- (b) Use of significant others as translators or interpreters is not recommended because of role conflicts or inability to communicate complex medical terminology.
  - (c) Cancer-related Spanish-language literature is available through the National Cancer Institute ([www.cancer.gov](http://www.cancer.gov)) and the American Cancer Society ([www.cancer.org](http://www.cancer.org)). Language preference can be toggled for these resources.
- (6) Offer explanations for any misconceptions concerning diagnosis, treatment, and follow-up care using teach-back techniques (AHRQ, 2020b).
  - (7) Perform and document a learning needs assessment that addresses cultural and religious beliefs and preferences and the desire and motivation to learn. The assessment should also include emotional, physical, cognitive, and communication barriers and limitations (Joint Commission, 2021).
  - (8) Assess patients individually and tailor teaching to their level of understanding. Use short and simple words, chunking (short sections of information), active voice, and concrete examples (AHRQ, 2020a; Cancer Patient Education Network, 2013; Joint Commission, 2021; Office of Disease Prevention and Health Promotion, 2015). Cancer-related literature for low-literacy patients is available through the National Cancer Institute ([www.cancer.gov](http://www.cancer.gov)) and the American Cancer Society ([www.cancer.org](http://www.cancer.org)).
  - (9) Engage patients in the learning process with patient portals, interactive educational activities, shared decision-making, and patient-reported outcome measurement.
  - (10) Effective care coordination and transition may be facilitated through handoff tools to improve continuity of care and collaboration between professionals. Patient navigators can be an effective link for patient and healthcare provider communication and satisfaction.
  - (11) Cultural respect is a strategy that enables organizations to work effectively in cross-cultural situations.
    - (a) Developing and implementing a cultural competency framework in health systems is an extended process that ultimately reduces health disparities and improves access to high-quality health care.
    - (b) Cultural respect benefits consumers, stakeholders, and communities.
    - (c) Because several elements can influence health communication (e.g., behaviors, language, customs, beliefs, perspectives), cultural respect is also critical for achieving accuracy in medical research (National Institutes of Health, n.d.).
3. Barriers to educator effectiveness (AHRQ, 2020b; Blecher et al., 2016)
    - a) The educator's expertise regarding the information provided
    - b) The educator's understanding of teaching-learning principles
    - c) The educator's understanding of differences in learning styles
    - d) The methods available to the educator for patient education
    - e) The educator's ability to match the appropriate teaching methods and language to specific content and learning styles; the language must be adapted to individual learning abilities, healthcare-related literacy, and ability to speak, read, and understand English.
    - f) The educator's ability to involve individuals in the learning process
    - g) The educator's ability to communicate with other members of the healthcare team to provide continuity of care between the various points of care (e.g., hospital, physician practice, home, extended-care facilities)
    - h) The decreased length of hospital stay and the increased need to deliver complex information to patients
- E. Methods of patient education (Blecher et al., 2016; Hopmans et al., 2014; Laszewski et al., 2016; LeFebvre & Felice, 2016; Neuss et al., 2016; Şahin & Ergüney, 2016; Sullivan et al., 2016)
1. Educational methods should be selected based on preferences and abilities. They may include any combination of the following:
    - a) Auditory, such as audiotapes, podcasts, or face-to-face live presentations
    - b) Printed or visual materials, including animations, three-dimensional graphics, educational videos, booklets, chemotherapy cards, infographics, and printed instructions regarding procedures or self-care measures
    - c) Computer-based learning using three-dimensional interactive animations, compact

- discs, flash drives, preloaded devices, screen sharing, or e-gaming
  - d) Web-based learning, including patient portals, learning management systems, and reliable external websites
    - (1) National Cancer Institute ([www.cancer.gov](http://www.cancer.gov))
    - (2) American Cancer Society ([www.cancer.org](http://www.cancer.org))
    - (3) American Society of Clinical Oncology ([www.cancer.net](http://www.cancer.net))
  - e) Demonstration and tactile methods using models
2. Patient education in any format includes teach-back techniques to reinforce learning and document strategies.
    - a) If the patient cannot teach back the message, a different mode of education should be considered when reteaching.
    - b) For example, if the original message was conveyed orally, visualization or interactive modes of education should be considered in follow-up efforts.
  3. Patient education is the responsibility of all nurses and the entire healthcare team and continues as an ongoing process throughout the cancer care continuum (American Nurses Association, 2015).

#### F. Scope of information

1. Provide easily understandable verbal, video, audio, written, or web-based information (AHRQ, 2020b; Frentos, 2015; Iowa Health System et al., 2017; Narwani et al., 2016; Truccolo, 2016).
  - a) If printed material is used, ensure that the sentences and paragraphs are short.
  - b) Bullet points are helpful.
  - c) Always encourage patients and significant others to ask questions, provide feedback, and participate actively.
2. Use the chunk and check method (AHRQ, 2020a).
  - a) Do not wait until the end of the visit to initiate teach-back.
  - b) Chunk out information into small segments and have your patient teach it back.
  - c) Repeat several times during a visit.
  - d) This method minimizes the likelihood of overwhelming the learner.
3. Include patients and significant others, and provide education on the following topics (Gumusay et al., 2016; LeFebvre & Felice, 2016; Neuss et al., 2016; Şahin & Ergüney, 2016; Sullivan et al., 2016):
  - a) Disease and treatment plan
  - b) Goals of treatment
  - c) Duration and schedule of treatment
  - d) Cancer medication names, including generic and brand names; the dose and frequency of the

treatment and number of cycles (length of therapy); and the implications and plan for missed or delayed doses, especially with the use of oral anticancer medications

- e) Supportive care medications, including generic and brand names, and their dose and frequency
  - f) Drug–drug and drug–food interactions based on the most current medication list
  - g) Potential short- and long-term adverse effects and the subsequent management strategies
  - h) Contact information for and directions regarding communicating with healthcare team members
  - i) Symptoms that require immediate discontinuation of self-administered medications or treatments
  - j) Procedures for handling medications in the home, including safe storage, handling, and management of unused medication
  - k) Procedures for handling body secretions and waste in the home
  - l) Procedures for disposing of medical waste sharps per state or local guidelines
  - m) Follow-up schedules, including laboratory and healthcare provider visits
  - n) A list of credible resources where more information can be obtained if desired
4. Encourage patients to write down questions between visits and bring them to follow-up appointments. At each visit, healthcare providers should address patient and caregiver questions.
  5. Use tools such as the Patient Education Materials Assessment Tool (PEMAT) to evaluate patient education materials (AHRQ, 2020c)

#### G. Documentation

1. Nurses assess and document patient understanding of the education provided (Joint Commission, 2021).
2. Documentation of understanding includes the patient's ability to verbalize or demonstrate learning and the need for information reinforcement. If patients cannot comprehend the information or refuse education, this must be documented with alternative plans.
3. Methods of assessing patient (and significant other) understanding include the following (Iowa Health System et al., 2017; Joint Commission, 2021):
  - a) The patient or their significant other communicates an understanding of the information presented, including medication names and the purpose of the therapy.
  - b) The patient or their significant other identifies crucial instructions for self-care.
  - c) The patient or their significant other identifies symptoms and side effects to report and how to contact the providers if needed.



- d) The patient brings new prescriptions to a follow-up visit and correctly states the instructions for use.
- e) The patient performs a return demonstration of procedures, such as temperature monitoring and handwashing.
- f) The patient or their significant other accurately identifies the date and time of the next follow-up visit.
- g) For oral agents, the patient or their significant other verbalizes the name of the medication, the correct procedure for administration (e.g., with or without food), and safe handling and disposal procedures. See Chapter 4 for a discussion on adherence to oral antineoplastics.
- h) The patient or their significant other shares where or how to obtain additional information if desired.
- i) The patient or their significant other communicates the need for additional teaching sessions if issues are identified or if complex or multimodal treatments are planned.

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## SECTION II

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# Cancer and Cancer Treatment

Chapter 4. Overview of Cancer and Cancer Treatment

Chapter 5. Clinical Trials and Drug Development



## CHAPTER 4

# Overview of Cancer and Cancer Treatment

### A. Definition of cancer

1. Cancer is fundamentally a disease of genomic alteration.

a) Hanahan and Weinberg proposed the hallmarks of cancer as a framework to describe eight functional characteristics acquired by cancer cells during tumorigenesis (Devita et al., 2020; Hanahan & Weinberg, 2011; see Table 4-1).

- (1) Sustained proliferative signaling
- (2) Evading growth suppressors
- (3) Resisting cell death
- (4) Enabling immortality
- (5) Inducing angiogenesis
- (6) Activating invasion and metastasis
- (7) Reprogramming energy metabolism
- (8) Evading immune response

b) The authors further described the developmental processes which foster the actuation of the original eight functional characteristics with enabling and emerging characteristics (Hanahan, 2022; Hanahan & Weinberg, 2011).

- (1) Genome instability
- (2) Tumor-promoting inflammation
- (3) Unlocking phenotypic plasticity
- (4) Nonmutational epigenetic reprogramming
- (5) Polymorphic microbiomes
- (6) Senescent cells

2. Theories of cancer origins (Eggert, 2018)

a) Clonal theory: Initial DNA changes result in benign growth, from which cloned cells accumulate multiple genomic alterations over time, resulting in malignancy.

b) Cancer stem cell theories

- (1) In the cancer stem cell model, cancer cells arise from cancer stem cells, which may have limited proliferative capability, and at least one cell line becomes tumorigenic.
- (2) The plasticity model builds on the cancer stem cell model, suggesting that noncancer stem cell versions of cells can change

throughout their life cycle and are converted to cancer stem cells.

c) Inflammation theory: Chronic inflammation is a prolonged immune response triggered by persistent infection, hypersensitivity disease, and long-term exposure to toxic agents, leading to tissue damage and ultimately cancer (e.g., hepatitis B infection leading to liver cancer).

3. Cancer genome

a) Cancer is a disease in which cells begin to divide and grow uncontrollably through genomic alterations in specific genes (Sanchez-Vega et al., 2018).

b) Abnormal behaviors demonstrated by cancer cells result from a cascade of pathogenic variations or alterations (formerly known as mutations) in the DNA of two types of key regulatory genes.

- (1) Proto-oncogenes encode for protein products that stimulate cell growth and division. In their natural state, or wild-type, these genes are known as proto-oncogenes; when DNA is altered, they become oncogenic and drive cancer growth.

- (2) Tumor suppressor genes encode for protein products that inhibit cellular division, repair damaged DNA, and promote apoptosis (programmed cell death) for damaged or aging cells. When altered, these genes become inactivated and allow uncontrolled cancer growth.

c) Oncogenic genes, known as driver variants, are activated during carcinogenesis. Many are genes that govern growth factors, growth factor receptors, and cell signaling and, when altered, continuously send signals to the nucleus of the cell to grow and divide (see Table 4-2).

d) Passenger variants, in contrast to driver variants, arise during carcinogenesis and do not contribute directly to disease.

e) Pathogenic variants inactivate tumor suppressor genes during carcinogenesis. Tumor sup-

**TABLE 4-1.** Hallmarks of Cancer

| Hallmark                           | Healthy Cells                                                                                                                                                                                                                     | Cancer Cells                                                                                                                                                                                                       | Example                                                                                                                                                                                                                                                                                                      |
|------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Proliferative signaling            | Healthy cells rely on external growth factor signaling to grow and maintain homeostasis.                                                                                                                                          | Cancer cells have the ability to sustain continuous growth signaling and do not require external stimulation to proliferate.                                                                                       | BRAF is a protein involved in directing cellular growth. Pathogenic variants in BRAF are therapeutic targets in treating melanoma and colon cancer.                                                                                                                                                          |
| Evading growth suppression         | Cells react to signals from tumor suppressor genes and contact inhibition to govern growth and division; growth suppression is regulated by a group of enzymes known as cyclin-dependent kinases.                                 | Cancer cells evade anti-growth signals by suppressing the retinoblastoma protein and other proteins, which leads to the continuous activation of cyclin-dependent kinases.                                         | Cyclin-dependent kinase 4/6 inhibitors reduce the activity of cyclin-dependent kinases and restore the growth suppression properties of the retinoblastoma protein.                                                                                                                                          |
| Resisting cell death               | Apoptosis is preprogrammed cellular death for damaged or aging cells.                                                                                                                                                             | Cancer cells evade apoptosis pathways to divide and grow uncontrollably.                                                                                                                                           | The <i>TP53</i> gene is responsible for repairing DNA damage; if repair is not possible, apoptosis is induced. Clinical trials targeting <i>TP53</i> dysfunction in cancer are ongoing.                                                                                                                      |
| Enabling immortality               | Cells are programmed with a limited number of growth-and-division cycles; DNA sequences called telomeres, located at the ends of chromosomes, control the cell division limit through a shortening process leading to cell death. | Cancer cells become immortal, reversing the telomere shortening process with the enzyme telomerase.                                                                                                                | Telomerase reverse transcriptase (TERT), an enzyme that reactivates telomerase, is being pursued as a direct therapeutic target. Clinical trials are ongoing.                                                                                                                                                |
| Inducing angiogenesis              | Angiogenesis is how new blood vessels are formed, which occurs only when needed during fetal development, menstrual cycle, and wound healing.                                                                                     | The growth of a vascular network is necessary for metastasis, as cancer cells require a supply of nutrients and oxygen and a system for waste removal.                                                             | Vascular endothelial growth factor is a cytokine that stimulates vascular endothelial cells to form new blood vessels under normal conditions and in tumor angiogenesis. It is a crucial therapeutic target in the development of antiangiogenic therapies.                                                  |
| Activating invasion and metastasis | Unlike blood cells, other cells cannot travel throughout the body, are governed by contact inhibition, and do not invade other tissue.                                                                                            | Invasion is the direct extension and penetration by cancer cells into neighboring tissue. Metastasis is the ability of the cancer cells to penetrate lymph and blood vessels to migrate and invade distant tissue. | Alterations in the <i>MET</i> gene lead to tumor cell proliferation, migration, and survival and are therapeutic targets in the treatment of non-small cell lung cancer.                                                                                                                                     |
| Reprogramming energy metabolism    | Cells generate energy through the orderly process of glycolysis, the Krebs cycle, and electron transport.                                                                                                                         | Cancer cells rely on glycolysis alone for energy production; in the presence of oxygen, cancer cells reprogram glucose metabolism by aerobic glycolysis, known as the Warburg effect.                              | Mechanistic target of rapamycin is a protein kinase that balances nutrient and energy availability with cellular growth and is involved in the Warburg effect. These inhibitors are used to treat renal cell carcinoma and are being studied in other cancers.                                               |
| Evading immune destruction         | Healthy cells develop immune checkpoints to protect against autoimmunity.                                                                                                                                                         | Cancer cells exploit these immune checkpoints to evade immune detection and elimination                                                                                                                            | Monoclonal antibodies block immune checkpoint proteins, programmed cell death protein 1, programmed cell death-ligand 1, and cytotoxic T-lymphocyte antigen 4. The immune system overcomes cancer's ability to resist immune responses and stimulates the body's mechanisms to defend itself against cancer. |

Note. Based on information from Devita et al., 2020; Hanahan & Weinberg, 2011.



**TABLE 4-2.** Oncogenic Driver Variants

| Oncogene                                       | Function                                                                                                               | Tumor Types                                                                |
|------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| <i>ABL</i>                                     | Increases cell proliferation                                                                                           | Chronic myeloid leukemia                                                   |
| <i>BCL2</i>                                    | Regulates apoptosis                                                                                                    | Lymphoma                                                                   |
| <i>BRAF</i>                                    | Controls growth signaling in MAPK pathway                                                                              | Colorectal and gastric cancer and melanoma                                 |
| Epidermal growth factor receptor (EGFR; ERBB1) | Cell surface receptor that activates signaling pathways within the cell, promoting cell growth, division, and survival | Amplified in colorectal, lung, breast, head and neck, and prostate cancers |
| HER2 (ERBB2)                                   | Cell surface receptor that activates signaling pathways within the cell, promoting cell growth, division, and survival | Amplified in breast, gastric, lung, and colorectal cancers                 |
| <i>MET</i>                                     | Regulates cell growth and motility                                                                                     | Papillary renal cell and lung cancer                                       |
| <i>MYC</i>                                     | Family of regulator and transcription genes that control cell division and malignant formation                         | Burkett lymphoma                                                           |
| <i>RAS</i>                                     | Family of genes that govern signaling pathways in cells                                                                | KRAS and NRAS: colorectal and lung cancer<br>NRAS: melanoma                |
| <i>RET</i>                                     | Cell signaling from outside and inside of the cell that promotes growth and maturation                                 | Thyroid and multiple endocrine neoplasias                                  |

Note. Based on information from Devita et al., 2020; Wilkes, 2018.

pressor genes are associated with DNA repair, limit cell division, and control apoptosis (see Table 4-3).

- f) Cancer cells are highly diverse or heterogeneous and contain many different types of DNA damage which constantly accumulate within the cancer genome.
- (1) Both large and small alterations can impact cellular behavior.
  - (2) Damage in the genes associated with DNA repair causes further genomic instability, leading to errors. These errors include

missense, nonsense, and frameshift variants; DNA deletions; translocations; amplifications; and mismatched nucleotide pairs, which accumulate and result in malignancy.

- g) Epigenetic changes (changes in genetic expression rather than DNA sequence) can affect the efficacy of DNA repair genes, altering specific gene expression and disrupting healthy expression of proto-oncogenes and tumor suppressor genes (e.g., DNA methylation).
  - h) Somatic cancer versus hereditary (germline) cancer
    - (1) Most pathogenic alterations accumulate throughout the lifetime of human somatic cells, leading to sporadic cancer.
    - (2) A small percentage of cancers, approximately 5%–10% depending on cancer type, are caused by germline pathogenic variants of tumor suppressor genes, which are inherited DNA changes passed between generations in the germ line (sperm and ova) (National Cancer Institute [NCI], 2017).
4. Multiple factors often interact, leading to the development of cancer. Healthy cells may change because of the following:
- a) Spontaneous transformation: No causative agent is identified, but cellular traits are characteristic of cancer cells.
  - b) Chronic or occupational exposure: Substances such as asbestos, benzene, radiation, tobacco, arsenic, nickel, and some chemotherapy agents are implicated in cancer development.
  - c) Changes in the microenvironment: Cancer cell plasticity, immune cell and signaling molecule involvement, and metabolic changes brought about by changes in oncogenes and tumor suppressor genes all contribute to the progression of cancer growth (Eggert, 2018).
  - d) Exposure to viruses: Genetic changes can occur to cells through viral infections (e.g., human papillomavirus [HPV] is the primary cause of cervical cancer) (Inan et al., 2017).

- B. The Cancer Care Continuum framework illustrates the various stages and pathways of patient care (Young et al., 2020).
1. Healthy lifestyles and the early detection of cancer can prevent up to 50% of cancers.
  2. Diagnosis and shared decision-making between the healthcare team, patient, and family help determine the treatment plan and goals of care.
  3. Goals of cancer therapy

**TABLE 4-3.** Tumor Suppressor Genes

| Tumor Suppressor Gene                | Function                                                                                              | Associated Hereditary Cancer Syndromes                       |
|--------------------------------------|-------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|
| <i>APC</i>                           | Controls cell division and contact inhibition                                                         | Familial adenomatous polyposis                               |
| <i>ATM</i>                           | Controls rate of cell growth and repairs damaged DNA                                                  | <i>ATM</i> -associated breast cancer                         |
| <i>BRCA1, BRCA2</i>                  | DNA repair genes                                                                                      | Hereditary breast, ovarian, prostate, and pancreatic cancers |
| <i>CDK4</i>                          | Controls progression through G <sub>1</sub> phase of cell cycle                                       | Melanoma                                                     |
| <i>MSH2, MSH6, MLH1, PMS2, EPCAM</i> | Mismatch repair genes                                                                                 | Hereditary nonpolyposis colon cancer (Lynch syndrome)        |
| <i>RB1</i>                           | Controls cell cycle                                                                                   | Retinoblastoma                                               |
| <i>TP53</i>                          | Most common altered gene in cancer; guardian of the genome; detects DNA damage and triggers apoptosis | Li-Fraumeni syndrome and many solid tumors                   |

Note. Based on information from Devita et al., 2020; Wilkes, 2018.

- a) Treatment planning includes shared decision-making that integrates the patient's personal goals, needs, and values as part of care planning (Cranley et al., 2017).

- b) Prevention (Mahon, 2018)

- (1) Primary cancer prevention includes measures taken to avoid carcinogen exposure and promote health or prevent disease development. Examples include avoidance of tobacco products and immunization against HPV.

- (a) Chemoprevention may include tamoxifen for women at risk for breast cancer or HPV vaccination to protect against HPV infection, which can cause cancers of the cervix, vagina, penis, anus, and oropharynx.

- (b) Lifestyle and behavioral modification of risk factors, including dietary choices, obesity, and smok-

ing, are associated with the development of some cancers (Smith et al., 2018).

- (2) Secondary cancer prevention includes early detection and treatment of cancer (e.g., mammogram, colonoscopy).

- (3) Tertiary cancer prevention includes monitoring for or preventing recurrence of the original cancer or second malignancies (e.g., rehabilitation and exercise programs, nutritional changes, psychosocial support) (Smith et al., 2018).

- c) Curative intent is a treatment that has the potential to eliminate disease (American Cancer Society [ACS], 2019a).

- d) Control is when a cure is not possible. The goal may be to administer treatment to slow the growth or spread of cancer and allow patients to live longer than if therapy had not been given (ACS, 2019a).

- e) Palliation is an interprofessional team-based approach that improves the quality of life for patients and families through expert assessment and treatment of physical, spiritual, psychological, and social problems associated with severe illness (World Health Organization [WHO], n.d.).

4. Cancer treatment and palliative care, which includes many cancer treatment modalities, uses as a monotherapy or combination therapy approach.

- a) Types of cancer treatment modalities include surgery, radiation therapy, chemotherapy, hormone therapy, immunotherapy, gene therapy, targeted therapy, and hematopoietic stem cell transplantation.

- b) Palliative care should be integrated early into treatment plans and is key to effective patient management. It can be provided in many care settings, including inpatient, outpatient, primary care, and community settings (WHO, n.d.).

5. Post-treatment care is referred to as *survivorship care* (NCI, n.d.-b).

- a) Practicing cancer prevention and making healthy lifestyle choices

- b) Providing follow-up cancer screenings

- c) Addressing physical and psychosocial late effects of treatment

- d) Rehabilitating with monitoring and management of long-term treatment effects

- e) Assessing for concerns such as financial toxicity and disability

- f) Transitioning to primary care management and referring to other specialists if indicated

6. End-of-life care encompasses symptom management and remembrance.

C. Cancer staging and grading (American College of Surgeons, n.d.; Amin et al., 2017; Vogel, 2018)

1. Staging

- a) Staging verifies the extent of the disease by assessing the location and size of the primary tumor and determining if it has spread to other tissues or organs.
- b) It informs prognosis, treatment planning, identification of suitable clinical trials, and treatment response.
- c) Staging conventions provide a common language that the healthcare team can use to communicate about a patient's case.
- d) Criteria are unique for many types of cancer (American College of Surgeons, n.d.; NCI, 2015).
- e) Four types of staging exist (American College of Surgeons, n.d.; Amin et al., 2017).
  - (1) Clinical: based on physical examination, imaging, and biopsy
  - (2) Pathologic: Based on tissue, fluids, or exploration during surgery; is combined with clinical staging
  - (3) Post-therapy/post-neoadjuvant therapy: used for confirming cancer remaining after systemic chemotherapy or hormone therapy, radiation therapy prior to surgery, or when no surgery is performed
  - (4) Restaging: used for determining the extent of recurrence; helpful for planning future treatment options
- f) The tumor, node, metastasis (TNM) staging system is maintained by the American Joint Committee on Cancer and the Union for International Cancer Control. It is the most commonly used anatomic staging system and is based on specific criteria. It is combined with a staging number (0–IV) and sometimes with substage classifications (e.g., IIa, IIb). In general, stage I confers a more favorable prognosis than stage IV (American College of Surgeons, n.d.; Amin et al., 2017; Vogel, 2018; see Figure 4-1).
- g) Hematologic malignancies, malignant melanoma, brain cancers, and other cancers are staged according to different systems (American Brain Tumor Association, n.d.; Leukemia and Lymphoma Society, n.d.-a, n.d.-b; Multiple Myeloma Research Foundation, 2021; Vogel, 2018).
  - (1) The Ann Arbor staging system is used to stage Hodgkin lymphoma.

- (2) The Rai staging system is used to stage chronic lymphocytic leukemia.
- (3) The International Staging System is used for multiple myeloma.

2. Grading

- a) Cellular differentiation is based on how closely tumor cells resemble healthy cells in structure and maturity.
- b) Differentiation is graded from GX (cannot be assessed) to G4 (undifferentiated, where the parent cell is impossible to distinguish).
  - (1) Grade 1 tumor cells appear very similar to healthy cells. They are referred to as low grade or well differentiated.
  - (2) Grade 2 tumor cells show more differences from healthy cells. They are referred to as intermediate grade or moderately differentiated.
  - (3) Grade 3–4 tumor cells have minimal similarities to healthy cells and are considered high grade or poorly differentiated.
- c) Cells are obtained by biopsy or surgical removal for microscopic examination by a pathologist. Cancer cell differentiation can vary over time, and cells with several differentiation grades can exist within a single tumor.
- d) Tumor grade is a prognostic indicator used in treatment planning. A higher grade indicates a more aggressive tumor (Vogel, 2018).

D. Cancer treatment modalities

1. Table 4-4 summarizes the history and evolution of antineoplastic therapy.
2. Surgery (Lester, 2018)
  - a) Surgery is a precise local treatment. It may be robotic assisted (Doyle-Lindrud, 2015).
  - b) Surgery may remove all or a portion of the primary tumor, lymph nodes, and adjacent tissues.
  - c) It can be used to obtain specimens for cytopathology.
  - d) Surgery may be the only treatment a patient requires.
  - e) It may be preceded by (neoadjuvant) or followed by (adjuvant) modalities, such as chemotherapy, immunotherapy, or radiation therapy.
  - f) Surgery may be used in the palliative setting to alleviate or lessen intolerable symptoms.
3. Radiation therapy (Behrend, 2018; Gosselin, 2018)
  - a) Radiation therapy is a local treatment in which energy is precisely aimed at a specific target.
  - b) It may be planned before surgery to decrease tumor burden (neoadjuvant) or after surgery (adjuvant) to prevent recurrence of the primary tumor.

**FIGURE 4-1.** Tumor, Node, Metastasis (TNM) Staging

| <b>T = tumor size</b>                                                                                                                                                                                 | <b>N = nodal involvement</b>                                                                                                                                                                                                                                                              | <b>M = metastasis</b>                                                                                                          |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>• TX = not assessed</li> <li>• Tis = in situ cancer</li> <li>• T0 = no primary tumor found</li> <li>• T1, T2, T3, T4 based on the tumor size/extent</li> </ul> | <ul style="list-style-type: none"> <li>• NX = not assessed</li> <li>• N0 = no lymph nodes involved</li> <li>• N1, N2, N3 based on the number/location of lymph nodes involved</li> <li>• Nmi = micrometastasis in the node</li> <li>• N(i-) = isolated tumor cells in the node</li> </ul> | <ul style="list-style-type: none"> <li>• MX = not assessed</li> <li>• M0 = no metastasis</li> <li>• M1 = metastasis</li> </ul> |

A patient's TNM stage may also have one or more letters at the beginning. These letters indicate when staging occurred.

- **cTNM** or **TNM**: No letter or a "c" indicates a clinical staging.
- **pTNM**: A "p" indicates a pathologic staging.
- **ycTNM**: A "yc" indicates a clinical staging following systemic or radiation therapy.
- **ypTNM**: A "yp" indicates a pathologic staging following systemic or radiation therapy.
- **rTNM**: An "r" indicates staging following a recurrence of cancer.
- **aTNM**: An "a" is used for staging cancer that was found during an autopsy.

Note. Based on information from American College of Surgeons, n.d.; Amin et al., 2017.

- c) This therapy is more effective for some diseases than others.
- d) Multiple treatment delivery methods exist, including various external beam treatments, stereotactic radiosurgery, image-guided CyberKnife® radiosurgery, brachytherapy, and sealed and unsealed radionuclide therapy.
- e) It is often given in combination with other antineoplastic therapies and termed chemoradiation or radioimmunotherapy, depending on the classification of the concurrent treatment.
4. Chemotherapy is the most traditional systemic cancer therapy (Dowling et al., 2017; see Chapter 6).
  - a) Chemotherapy is most commonly administered as a systemic treatment.
  - b) It may be used locally for instillations (e.g., bladder, peritoneum) or as a topical therapy.
  - c) Chemotherapy may be used as a single agent or, more commonly, in combination.
  - d) It may be dose limiting from cytotoxic effects on healthy tissues.
  - e) This therapy disrupts the cell cycle at different points, triggering cellular death.
  - f) It is used in high doses for hematopoietic stem cell transplantation.
  - g) Examples include alkylating agents, antimetabolites, antitumor antibiotics, nitrosoureas, and plant alkaloids (e.g., taxanes, vinca alkaloids, camptothecins).
5. Hormone therapy (Tortorice, 2018; see Chapter 7)
  - a) Hormone therapy is a systemic treatment, often combined with other antineoplastic agents. It can be oral or injectable.
  - b) It has various mechanisms of action and unique side effect profiles.
  - c) Examples include corticosteroids, androgens, antiandrogens, selective estrogen receptor modulators, estrogen receptor antagonists, aromatase inhibitors, and luteinizing hormone-releasing hormone antagonists and agonists.
6. Immunotherapies and gene therapies (Bayer et al., 2017; Lea, 2018; Martin, 2017; Muehlbauer et al., 2018; Vioral, 2018; see Chapter 10)
  - a) Immunotherapies and gene therapies are systemic treatments that use the patient's immune system through various pathophysiologic mechanisms.
  - b) They may be synthetic (e.g., chimeric antigen receptor T cells), biologically derived (e.g., monoclonal antibodies), or nonpathogenic or pathogenic virus (requiring modification for use).
  - c) Examples include chimeric antigen receptor T-cell therapies, checkpoint inhibitors, monoclonal antibodies, cancer vaccines, immunomodulators, cytokines, and oncolytic viruses.
  - d) These therapies cause significant cytokine release syndrome, hypersensitivity reactions, and other unique side effects because of the immune response to the drug.
  - e) This is a rapidly developing class of treatment options.
  - f) Gene therapies typically correct defective genes by inserting a healthy gene into the nuclei of abnormal cells to repair, replace, or alter its function through viral vectors.
  - g) Biosimilars are biologic products similar to, but not the same as, the reference drug they mimic.
    - (1) Biosimilar drugs have no clinically meaningful differences from the reference product.
    - (2) They are not generic forms of a reference drug (which are chemically identical to the reference drug) instead they are chemically similar, and structural and chemical changes should not affect efficacy (U.S. Food and Drug Administration [U.S. FDA], 2021b).

- (3) Biosimilars are produced through an abbreviated manufacturing process and are expected to be an affordable alternative to some therapy agents.
7. Targeted therapies (Devita et al., 2020; Wilkes, 2018; see Chapter 8)
- Targeted therapies are treatments that act on key altered oncogenes or tumor suppressor genes (see Table 4-5).
  - Key oncogenes encode for protein kinases, are involved in signaling pathways, are sensitive to pharmacologic inhibition, and are actionable therapy targets.
  - Genomic alterations have become highly sensitive, and specific biomarkers for disease detection, monitoring, and treatment selection have been identified to select appropriate targeted therapy.
- d) Targeted agents include tyrosine kinase inhibitors, anaplastic lymphoma kinase inhibitors, cyclin-dependent kinase inhibitors, and epidermal growth factor receptor inhibitors. Many other targets exist, and most of these agents are oral.
- e) Unlike traditional chemotherapy, which disrupts cellular division in healthy and cancer cells, targeted agents affect only altered cancer cells, minimizing toxicity in nonmalignant cells (Wilkes, 2018).
8. High-dose chemotherapy with hematopoietic stem cell transplantation
- High-dose chemotherapy, with or without radiation, is administered with the intention of bone

**TABLE 4-4.** History of Cancer Treatments

| Period           | Events                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Pre-20th century | <p>In the 1500s, heavy metals were used systemically to treat cancers; however, their effectiveness was limited, and their toxicity was significant (Burchenal, 1977).</p> <p>Prior to 1890, surgical treatment or cauterization of tumors was the most common therapeutic option (Falzone et al., 2018).</p> <p>In the 1890s, William Coley developed and explored Coley toxins, the first nonspecific immunostimulants used to treat cancer.</p> <p>In 1899, Marie and Pierre Curie proposed using radiation to treat cancer (Falzone et al., 2018).</p>                                                                                                                                                                                                                                                                                                                                                                                                              |
| 1930–1940        | <p>The use of nitrogen mustard gas as a chemical weapon in World War I and the accidental use of this banned weapon in World War II led to the discovery of the first DNA alkylating agent, as its toxic effect led to bone marrow and white blood cell suppression. This discovery led to the use of chemotherapy to treat hematologic and solid tumors (Falzone et al., 2018). Alkylating agents became recognized as a successful treatment for lymphoma (Gilman &amp; Philips, 1946). Folic acid antagonists, later called methotrexate, were found to be effective against pediatric acute lymphoblastic leukemia (Farber et al., 1948).</p> <p>Congress passed the National Cancer Act in 1937, establishing the National Cancer Institute.</p>                                                                                                                                                                                                                   |
| 1950s            | <p>Research dedicated to nonhematologic cancers began with actinomycin-D in pediatric solid tumors (Falzone et al., 2018). The Children's Cancer Group (now part of the merged Children's Oncology Group) was formed as the first cooperative group dedicated to finding effective treatments for pediatric cancer.</p> <p>Metastatic choriocarcinoma was the first metastatic disease cured by treatment with methotrexate in 1956.</p> <p>The first bone marrow transplant was performed in 1956.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 1960–1970        | <p>Combined therapeutic protocols using several chemotherapy drugs with different mechanisms of action became the standard in clinical practice (Falzone et al., 2018).</p> <p>The Philadelphia chromosome was discovered in the cells of chronic myeloid leukemia. This genetic abnormality is a fusion gene called <i>BCR-ABL 1</i>, which continuously promotes cancer growth. This marked the beginning of the search for targeted therapies against this abnormal cancer cell behavior.</p> <p>Mechlorethamine, vincristine, procarbazine, and prednisone (MOPP), the first combination chemotherapy, were used and found to be curative against Hodgkin lymphoma (Noonan, 2007).</p> <p>Chemotherapy was used with surgery and radiation, beginning combination treatment for cancer.</p> <p>The development of hybridoma technology began leading to the discovery of monoclonal antibodies.</p> <p>Tamoxifen is synthesized in 1962 and first used in 1969.</p> |
| 1970s            | <p>The National Cancer Act of 1971 provided funding for cancer research.</p> <p>Adjuvant chemotherapy became a standard cancer treatment (Bonadonna et al., 1995; Fisher et al., 1986).</p> <p>The discovery of the human leukocyte antigen histocompatibility system expanded the use of and survival from bone marrow transplantation (Perry &amp; Linch, 1996).</p> <p>The <i>TP53</i> gene, the most commonly altered gene in human cancer, was discovered in 1979, beginning the search for the genetic basis of cancer.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                       |

(Continued on next page)



**TABLE 4-4.** History of Cancer Treatments (*Continued*)

| Period       | Events                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|--------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1980s        | <p>Community clinical oncology programs were developed in 1983 to contribute to National Cancer Institute chemotherapy clinical trials.</p> <p>Focus turned to symptom management to alleviate dose-limiting toxicities related to neutropenia, nausea and vomiting, and cardiotoxicity.</p> <p>Scientists investigated recombinant DNA technology, leading to treatments involving interferon alpha and erythropoietin. This marked the beginning of biotechnical advancements in cancer treatment (Devita et al., 2020).</p> <p>High-dose chemotherapy was used for myeloablation prior to bone marrow and stem cell transplantation (Perry &amp; Linch, 1996).</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| 1990s        | <p>New classifications of drugs (e.g., taxanes) were developed; paclitaxel was found to be effective against ovarian and breast cancers (Rowinsky et al., 1992).</p> <p>Biotechnical advancements continued with approvals of granulocyte-colony-stimulating factor and granulocyte macrophage-colony-stimulating factor, interleukin-2, interleukin-11, and the first cancer-directed monoclonal antibodies rituximab and trastuzumab.</p> <p>The approval and widespread use of ondansetron for the prevention of chemotherapy-induced nausea and vomiting had an enormous impact on symptom management, improved quality of life for chemotherapy patients, and allowed for the greater development of outpatient treatment protocols (Perez, 1995).</p> <p>Based on the studies by Mary-Claire King, the first tumor suppressor and breast cancer susceptibility gene, <i>BRCA1</i>, was sequenced in 1994. <i>BRCA2</i> was discovered the following year. These breakthroughs confirmed the genetic basis of some cancers (Gnarra et al., 1995; Hoskins et al., 1995; Miki et al., 1994).</p> <p>Aromatase inhibitors were approved for breast cancer treatment. This marked a step forward for hormone therapy.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 2000s        | <p>The U.S. Food and Drug Administration approved imatinib to treat chronic myeloid leukemia, the first targeted treatment that disrupts the action of the altered <i>BCR-ABL</i> gene (Falzone et al., 2018).</p> <p>The Human Genome Project was completed, meeting the goal of mapping and understanding of all the genes of human beings (Devita et al., 2020).</p> <p>Radioimmunotherapy was developed to deliver radioactivity directly to select tumor cells, avoiding damage to healthy tissue (e.g., ibritumomab tiuxetan, tositumomab, iodine-131).</p> <p>The U.S. Food and Drug Administration approved the following:</p> <ul style="list-style-type: none"> <li>• Bevacizumab is the first approved antiangiogenic agent for cancer (American Society of Clinical Oncology, n.d.-a).</li> <li>• Aprepitant, a neurokinin-1 antagonist, is used in combination with other antiemetic drugs to prevent chemotherapy-induced nausea and vomiting.</li> <li>• A prophylactic vaccine prevents human papillomavirus infections that cause cervical cancer (American Society of Clinical Oncology, n.d.-a).</li> <li>• Targeted therapies were developed to affect epidermal growth factor receptors in lung cancer (gefitinib and erlotinib) and colon cancer (cetuximab and panitumumab) (American Society of Clinical Oncology, n.d.-a).</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 2010–present | <p>In 2010, the Patient Protection and Affordable Care Act was signed into law.</p> <p>American cancer survivors numbered 13.7 million, the highest total to date (American Society of Clinical Oncology, n.d.-a).</p> <p>The U.S. Food and Drug Administration approved the following:</p> <ul style="list-style-type: none"> <li>• Sipuleucel-T was the first cancer treatment vaccine to use the patient's dendritic cells in the immune system to attack cancer cells (Anassi &amp; Ndefo, 2011).</li> <li>• The immunotherapy drug ipilimumab for unresectable or metastatic melanoma stimulates the body's immune system to attack cancer cells (Bristol-Myers Squibb, 2011; National Cancer Institute, 2015).</li> <li>• The first antibody-drug conjugate, ado-trastuzumab emtansine (T-DM1), links trastuzumab (the monoclonal antibody) with a microtubular inhibitor.</li> <li>• The first programmed cell death-ligand 1 checkpoint inhibitor, atezolizumab, is used to treat advanced bladder cancer (American Society of Clinical Oncology, n.d.-b).</li> <li>• Chimeric antigen receptor T-cell therapy is used for select patients with B-cell acute lymphoblastic leukemia. It is the first gene therapy that uses technology to reprogram the patient's immune system to destroy cancer cells (Novartis Pharmaceuticals, 2017).</li> <li>• Bevacizumab-awwb is the first biosimilar approved in the United States to treat cancer (U.S. Food and Drug Administration, 2017b).</li> <li>• Larotretinib was the first agent approved to treat a genetic variant, rather than the tumor location, marking the beginning of tumor agnostic therapies (Raez &amp; Santos, 2018).</li> <li>• By May 2021, more than 70 U.S. Food and Drug Administration–approved targeted agents were available to treat solid and hematologic malignancies based on biomarkers detected in the tumor (National Cancer Institute, 2020a).</li> </ul> |

marrow ablation, with subsequent rescue using peripheral, bone marrow, or umbilical stem cells.

- b) Transplants can be autologous, allogeneic, syngeneic, or haploidentical. High-dose chemotherapy with hematopoietic stem cell transplantation is the standard of care for many hematologic malignancies (Tortorice, 2018).

#### E. Treatment approaches

1. Chemoprevention uses selected pharmacologic agents to prevent cancer in high-risk individuals (e.g., tamoxifen for women whose personal health history indicates a statistically increased risk for developing breast cancer) (Smith et al., 2018).
2. Neoadjuvant therapy uses one or more treatment modalities before the primary treatment (e.g., chemotherapy before surgery). The goal is to debulk the primary tumor before surgery or address micrometastases (Tajima et al., 2017; Tortorice, 2018).
3. Adjuvant therapy follows the primary treatment modality (e.g., chemotherapy or radiation after surgery). The goal is to target minimal disease or micrometastases for patients at high risk for recurrence (Tortorice, 2018).
4. Conditioning or preparative therapy is the administration of chemotherapy, sometimes with total body irradiation, to eliminate residual disease or ablate the marrow space before receiving a hematopoietic stem cell transplantation (also referred to as myeloablation).
  - a) Myeloablative therapy includes the obliteration of bone marrow with chemotherapy agents that are typically administered in high doses in preparation for hematopoietic stem cell transplantation. This therapy does not allow for spontaneous marrow recovery because of the lethal doses of agents used; therefore, it must be followed by transplantation to prevent death (Zack, 2018).
  - b) Nonmyeloablative therapy is reduced-intensity conditioning using doses that are not lethal to bone marrow (Epperla et al., 2017). This type of transplant is dependent on the graft-versus-tumor effect.
5. Immunosuppression is the administration of anti-neoplastic agents at doses sufficient to blunt a patient's immune response. Agents such as methotrexate are given post-transplantation to prevent graft-versus-host disease. Select agents are used to treat noncancerous conditions, such as autoimmune diseases.

#### F. Treatment strategies

1. Over the past two decades, unprecedented advancements in molecular biology, genomics, and gene sequencing technology have led to a shift from tra-

ditional cancer treatments toward genomically guided care known as precision oncology (Devita et al., 2020).

2. Traditional cancer treatments are designed to remove solid tumors surgically and halt tumor growth through systemic disruption of mitotic division in all cells (through radiation or chemotherapy). This is accomplished via single or combination therapies (Haque et al., 2017; Jin et al., 2017; Mokhtari et al., 2017; Tortorice, 2018; Zhang et al., 2017).
  - a) Drug combinations or drug–therapy combinations (e.g., drug plus radiation therapy) provide superior efficacy and survival advantage over monotherapy in many tumor types and combination regimens.
  - b) The mechanism by which this occurs is not fully understood in some cases.
  - c) Hypotheses include that one agent may potentiate the effect of another or that the combined agents or therapies create effects that together are unique.

**TABLE 4-5.** Genomic Alterations Used to Select Treatment

| Genomic Alteration              | Disease Type With Approved Treatment                      |
|---------------------------------|-----------------------------------------------------------|
| <b>Oncogene Driver Variants</b> |                                                           |
| <i>ABL1</i>                     | Chronic myeloid leukemia and acute lymphoblastic leukemia |
| <i>ALK</i>                      | Lung cancer and melanoma                                  |
| <i>BRAF</i>                     | Melanoma and colorectal and lung cancers                  |
| <i>EGFR</i>                     | Lung cancers                                              |
| <i>ERBB2</i> (HER2)             | Breast, colorectal, endometrial, and gastric cancers      |
| <i>ESR1</i>                     | Breast cancers                                            |
| <i>KRAS</i>                     | Lung and colorectal cancers                               |
| <i>MET</i>                      | Lung cancers                                              |
| <i>NRAS</i>                     | Lung and colorectal cancers                               |
| <i>NTRK</i> fusions             | All solid tumors                                          |
| <i>PIK3CA</i>                   | Breast cancers                                            |
| <i>ROS1</i>                     | Lung cancers                                              |
| <b>Tumor Suppressor Genes</b>   |                                                           |
| <i>ATM</i>                      | Prostate cancers                                          |
| <i>BRCA1</i> and <i>BRCA2</i>   | Breast, ovarian, pancreatic, and prostate cancers         |

Note. Based on information from Devita et al., 2020; Wilkes, 2018.



- (1) Tumor cell populations are heterogeneous; therefore, a combination of agents or therapies with different mechanisms of action can increase the number of cells killed at any one time.
  - (2) Combination agents or therapies with different mechanisms of action also reduce the possibility of drug resistance, as researcher consensus concludes that many mechanisms of resistance are likely to be occurring within a single tumor (Mokhtari et al., 2017; NCI, 2016).
  - (3) Combinations of drugs can be used synergistically to access sanctuary sites. One drug's solubility or affinity for specific tissues may be different from, but complementary to, another particular drug's characteristics (Mokhtari et al., 2017).
  - (4) Drugs with similar toxicities generally are avoided; however, this is not always possible. Therapy combinations may potentiate the toxic effects of either or both therapies or may be lessened because of different targeted mechanisms of action (Mokhtari et al., 2017).
3. Dosing of cytotoxic chemotherapy
- a) Treatment cycles are designed to permit recovery from damage to healthy tissues and organs and are based on the known pharmacokinetics of agents. Because the average white blood cell nadir is 10–14 days, many regimens are based on this time frame (Drooger et al., 2016; Tortorice, 2018).
  - b) Dose density refers to the drug dose per unit of time. Higher dose density is achieved by shortening the intervals between treatments (Lambertini et al., 2017). Reducing the time between chemotherapy cycles may diminish tumor regrowth.
  - c) Dose intensity is the amount of drug delivered over time.
    - (1) Dose reduction or delay resulting from chemotherapy side effects, scheduling conflicts, or any other reason reduces dose intensity and may negatively affect patient survival (Matikas et al., 2017).
    - (2) The prophylactic use of a myeloid growth factor has allowed for the administration of dose-dense and dose-intense chemotherapy regimens that would otherwise result in unacceptable neutropenia (Matikas et al., 2017).
  - d) Relative dose intensity is calculated by comparing the received dose to the referenced (standard) dose. Proactively managing symptoms and educating patients on maintaining the prescribed dosing schedule are paramount to optimal outcomes (Matikas et al., 2017).
  - e) Dose density and intensity and relative dose intensity concepts may not apply to targeted therapies, immunotherapies, and hormone therapies because of different toxicity profiles.
4. Genomically guided treatment with molecular or genomic biomarkers
- a) Detecting protein biomarkers for estrogen and progesterone receptors through the immunohistochemistry staining technique was one of the earliest applications in patient management (Dai et al., 2016).
    - (1) The overexpression of estrogen receptors and progesterone receptors in breast cancer predicts the potential for a clinical response to hormone therapy.
    - (2) Estrogen receptor status is also a prognostic indicator in that patients with hormone receptor positivity generally have a more favorable prognosis (Dai et al., 2016).
  - b) Tumor-specific genomic alterations in driver genes, which promote growth and tumor formation, and some tumor suppressor genes are predictive biomarkers for response to targeted agents in the treatment of malignancy (Malone et al., 2020).
    - (1) DNA sequencing is a laboratory process used to learn the exact order (or sequence) of the four building blocks that make up DNA and find alterations that may cause diseases such as cancer (NCI, n.d.-c).
    - (2) The Cancer Genome Atlas was a collaboration between NCI and the National Human Genome Research Institute that resulted in the development of comprehensive maps of the key genomic changes taking place in 33 different types of cancer (NCI, n.d.-a).
    - (3) Specific variants in the tyrosine kinase signaling pathway lead to uncontrolled cell proliferation and tumor formation.
      - (a) By stimulating the downstream intracellular signaling process, these variants cause accelerated cell proliferation, extended cell survival, and increased angiogenesis.
      - (b) Biomarker testing for these variants can guide the prioritization of therapies specific to these receptors for patients most likely to benefit from a targeted agent. It can also identify

those who will not benefit from a targeted agent.

- (c) Numerous small molecule tyrosine kinase inhibitors have been designed to block phosphorylation and suppress tumor growth (Malone et al., 2020; Wilkes, 2018).

As of May 2021, more than 70 FDA-approved targeted agents exist to treat solid and hematologic malignancies based on biomarkers detected in the tumor (NCI, 2020b; see Chapter 8).

- c) Programmed cell death-ligand 1 (PD-L1) protein is found on healthy and cancer cells.

- (1) Overexpression of PD-L1 by tumor cells inactivates the body's immune activity against the cancer cell by binding with the programmed cell death protein 1 (PD-1) antigen on the T cell. By suppressing the T cell, the cancer cell can evade attack by the body's immune system.

- (2) Immunotherapy treatments that target either PD-L1 or PD-1 block this binding, keeping PD-L1 from inactivating the T cell and boosting the immune system in its response against the cancer cell (Bayer et al., 2017).

- (a) PD-1 inhibitors help treat several types of cancer, including melanoma, non-small cell lung cancer, kidney cancer, bladder cancer, head and neck cancer, and Hodgkin lymphoma.

- (b) PD-L1 inhibitors have effectively treated bladder cancer, non-small cell lung cancer, and Merkel cell carcinoma (ACS, 2019b).

#### G. Measuring response

1. The earliest measures of determining response date back to 1976. Since then, many tools and factors have been considered when measuring response. A gold standard for all tumor types is not used.
2. Objective tumor response and quantitative measurement
  - a) Objective tumor response is assessed through quantitative measurements, such as surgical examinations, imaging studies, or serum biomarkers.
  - b) Baseline measurements recorded at the time of diagnosis are compared to those recorded after treatment completion.
  - c) The Response Evaluation Criteria in Solid Tumors (RECIST) guidelines were published in 2000 by members of the European Organisation

for Research and Treatment of Cancer, NCI, and NCI of Canada. These guidelines addressed most of the deficiencies in the WHO criteria.

- (1) RECIST guidelines recommended the use of one-dimensional tumor measurements (the longest diameter) rather than the cross product (Bates & Fojo, 2019).

- (a) Complete response is the complete disappearance of the disease.

- (b) Partial response is a 30% or more significant reduction in the sum of the longest diameter of the target lesion.

- (c) Stable disease is a change that does not meet the criteria for response or progression.

- (d) Progression includes a 20% or more significant increase in the sum of the longest diameter of target lesions.

- (2) RECIST 1.1 was developed in 2009 as technology and medicine advanced. Using the same criteria for response as RECIST 1.0, it also identified and addressed its predecessor's issues. For example, criteria were updated to include nodal disease (Bates & Fojo, 2019). RECIST 1.1 also has known limitations, including the following (Persigehl et al., 2020):

- (a) The criteria depend solely on anatomic measurements and do not consider tumor vascularity or functional imaging parameters.

- (b) In 2017, iRECIST was published to include a modified set of response criteria to address therapy response patterns seen with immunotherapy.

- (c) Traditional cytotoxic chemotherapy often results in the reduction of tumor size. However, newer targeted agents that interfere with or inhibit cell growth and division by inhibiting molecular pathways are considered cytostatic, meaning they block tumor cell proliferation. In contrast, standard chemotherapy agents are cytotoxic, meaning they kill tumor cells.

- (d) Studies of several cancer types, such as prostate cancer, mesothelioma, soft tissue sarcoma, and neuroendocrine tumors, have also shown that RECIST 1.1 criteria are inaccurate in reporting response to therapy (Sandra-segaran, 2015).

3. Clinical benefit response
  - a) The concept of clinical benefit response was developed when patients did not have measurable tumor shrinkage but experienced a reduction in symptoms (e.g., pancreatic cancer).
  - b) Clinical benefit is a combination of reduction or improvement in pain, performance status, and weight (Bates & Fojo, 2019; U.S. FDA, 2018).
4. Pathologic complete response in high-risk, early-stage breast cancer is the end point used to evaluate response after neoadjuvant treatment.
  - a) After a standard neoadjuvant chemotherapy regimen, the breast is resected and evaluated for remaining breast cancer cells.
  - b) The absence of cancer cells in the resected breast is referred to as a pathological complete response (Bates & Fojo, 2019; U.S. FDA, 2020).
5. Computed tomography–based tumor density is frequently used with diseases that respond to treatment but have minimal tumor shrinkage, such as gastrointestinal stromal tumor, renal cell cancer, or hepatocellular cancer (Bates & Fojo, 2019).
6. Glucose analog tracer, fluorine-18 fluorodeoxyglucose positron-emission tomography
  - a) In 2007, the International Working Group incorporated guidelines using positron-emission tomography (PET) assessments in metabolically active lymph nodes. Although widely used in clinical trials as part of the standardized response criteria for lymphoma, PET imaging in solid tumors is used to detect new or recurrent disease sites. It can also be an adjunct for evaluating disease progression when using RECIST criteria (Bates & Fojo, 2019).
  - b) The most recent effort to standardize PET criteria is Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST 1.0) by the European Organisation for Research and Treatment of Cancer and NCI. PERCIST specifies that the percentage of change in metabolic activity from baseline to post-treatment scans be recorded to provide a continuous plot of tumor activity. However, because of variations in patient activity, carbohydrate intake, blood glucose, and timing of scans, the comparability of PET images remains a challenge (Bates & Fojo, 2019; O et al., 2016).
7. Monitoring biomarkers
  - a) Monitoring biomarkers are proteins that can be measured in the blood to indirectly evaluate cancer progression.
  - b) These biomarkers are most useful in monitoring response to a treatment or progression of disease.
  - c) The direction, whether future levels increase or decrease, and the rate of change allow the provider to determine treatment efficacy.
  - d) Therefore, it is helpful to obtain baseline biomarkers before the tumor is excised and before the initiation of treatment (U.S. FDA, 2021a).
8. Circulating tumor cells and circulating tumor DNA are indicated in some solid tumors (e.g., ovarian, non-small cell lung, breast, prostate) and under investigation in hematologic malignancies (NCI, 2020a).
  - a) The number of circulating tumor cells in the blood is prognostic, with higher levels conferring a poor prognosis.
  - b) The amount of circulating tumor DNA appears to correlate with tumor burden and increases with stage.
9. Immune-related response criteria
  - a) Several new therapy options are being studied and have been FDA approved to harness the immune system in controlling malignancy.
  - b) The patterns of response to treatment with immunotherapy agents differ from treatments with targeted therapies, hormone therapies, or cytotoxic agents in several important respects (Persigehl et al., 2020).
    - (1) Patients may have transient worsening of disease before it stabilizes or the tumor regresses; therefore, caution should be taken in discontinuing treatment early.
    - (2) Treatment response can take longer to become apparent than cytotoxic therapy.
    - (3) Some patients who do not meet the criteria for objective response can have prolonged periods of stable disease that are clinically significant.
  - c) The iRECIST criteria were developed to properly recognize these nontraditional patterns of response seen with checkpoint inhibitors and other immunotherapies. Without these criteria, the application of RECIST criteria in patients treated with checkpoint inhibitors may lead to premature discontinuation of treatment in those who will eventually respond to treatment or have prolonged disease (Persigehl et al., 2020).
    - (1) Immune-related complete response is the complete resolution of all lesions, with no new lesions. It must be confirmed by a consecutive assessment after at least four weeks.
    - (2) Immune-related partial response is a decrease in the total tumor burden of 50% or more compared to baseline, which

must be confirmed with a second assessment after at least four weeks. This allows for the inclusion of progression of some lesions or the appearance of new lesions as long as the total tumor burden meets the response criteria.

- (3) In immune-related stable disease, the tumor does not meet the criteria for a partial or complete response or progressive disease.
  - (4) Immune-related progressive disease is an increase in tumor burden by 25% or more relative to the minimum recorded tumor burden. It must be confirmed by a second assessment no less than four weeks after the initial documentation of an increase in the tumor.
10. Patient outcomes
- a) Direct evidence of treatment benefit is derived from clinical trial effectiveness end points that measure survival or meaningful aspects of how patients feel or function in daily life (U.S. FDA, 2017a).
    - (1) In the 1970s, FDA approved cancer drugs based on objective response rates determined by tumor assessments.
    - (2) However, in the 1980s, FDA determined that cancer drug approval should be based on more direct evidence of clinical benefits, such as improved survival, tumor-related symptoms, quality of life, or physical functioning (U.S. FDA, 2018).
  - b) Survival data are gathered to assess the efficacy of cancer treatment.
    - (1) The starting point for survival measurement may be the date of diagnosis, first visit to the physician or clinic, hospital admission, treatment initiation, or randomization to a clinical trial (Hess, 2017).
    - (2) The vital status of each patient is noted as alive, dead, or unknown. The status is recorded at the end point of participation in a study, including the completion of the study or when the individual is lost to follow-up or dies (Hess, 2017).
  - c) Tumor assessment (U.S. FDA, 2018)
    - (1) Time to progression and progression-free survival have also served as primary end points for drug approval. Time to progression is the time from randomization to progression, whereas progression-free survival is the time from randomization until disease progression or death.
    - (2) Disease-free survival is the time from randomization until tumor recurrence or death from any cause. This end point is most frequently used in the adjuvant setting after definitive surgery or radiation therapy.
    - (3) Objective response rate refers to the proportion of patients in a study with a reduction in tumor burden of a predetermined amount and for a minimum period. Response duration is measured from the initial response until documented tumor progression. Per FDA, if available, standardization criteria should be used to ascertain response (e.g., RECIST criteria has been considered appropriate).
    - (4) Time to treatment failure is the end point measuring time from randomization to discontinuation of treatment for any reason, including progression, treatment toxicity, or death.
  - d) Symptom assessment on quality of life
    - (1) The American Society of Clinical Oncology Cancer Research Committee stated, "In arriving at goals for clinical trials, both survival and quality of life were considered as important to outcomes that are clinically meaningful for patients" (Stenger, 2014, "Primary Goal," para. 1).
    - (2) The committee also stated that cancer progression symptoms and treatment tolerability are essential factors when considering whether a new treatment is associated with a clinically meaningful outcome (Stenger, 2014).
  - e) Performance status
    - (1) Performance status is the level of normal daily activity that patients can sustain to care for themselves. This includes their physical ability, such as walking and working. Performance status is affected by cancer, complications of cancer, and comorbid conditions (Scott et al., 2020).
    - (2) Assessing performance status is a way for physicians to track changes in a level of functioning due to cancer treatment. Documenting performance status using a standardized index allows clinicians to consistently report patient response to clinical trials (ECOG-ACRIN Cancer Research Group, n.d.).
    - (3) Commonly used measurements of performance status

- (a) Eastern Cooperative Oncology Group (ECOG) Performance Status Scale
  - i. First published in 1982, it is also called the WHO or Zubrod score. Key elements of the ECOG scale first appeared in medical literature in 1960 by C. Gordon Zubrod (Zubrod, 1984).
  - ii. This rating scale uses scores from 0 to 5, indicating poorer performance status as the score increases (ECOG-ACRIN Cancer Research Group, n.d.).
- (b) The Karnofsky Performance Status Scale was first introduced in 1949 with an index rating between 100 and 0, with a higher score indicating better performance (ECOG-ACRIN Cancer Research Group, n.d.).
- (c) The Lansky Play-Performance Scale for Pediatric Patients classifies patients younger than age 16 years. The form is completed by parents based on the child's activity over the past week and is repeated over time to assess for changes in performance status (Lansky et al., 1987).
- (d) Table 4-6 compares the three performance rating scales.

#### H. Factors affecting treatment response

1. *Comorbidity* refers to the coexistence of disorders in addition to a primary disease of interest (Fowler et al., 2020).
  - a) In one large-scale population-based study, up to two-thirds of patients had at least one chronic condition at the time of cancer diagnosis, and half of these patients had multiple comorbidities (Fowler et al., 2020).
  - b) Comorbidity has consistently been found to negatively impact cancer detection, treatment, treatment adherence, and overall survival (Fowler et al., 2020).
  - c) Patients with comorbidities are less likely to receive adjuvant therapy, more likely to receive a reduced dose, and less likely to complete a course of treatment (Fowler et al., 2020).
  - d) Cancer or its treatment may affect comorbidity outcomes. Antineoplastic therapies can increase the risk of cardiovascular, metabolic, musculoskeletal, and other conditions and can worsen preexisting comorbidities (Fowler et al., 2020).
2. According to NCI (n.d.-d), tumor burden is the number of cancer cells, the size of the tumor, or the

amount of cancer in the body. The larger the tumor (sometimes referred to as the bulkiness of the disease), the greater the chance of spreading and developing metastatic disease.

3. The genomic instability of the tumor cell and the emergence of drug resistance are currently considered the most significant determination of response (Tortorice, 2018).

a) Temporary or relative resistance is usually a function of the drug's inability to reach the target cell. Causes of temporary resistance include the following (Tortorice, 2018):

- (1) Poor blood supply
- (2) Anatomic sanctuary sites (e.g., testes, central nervous system)
- (3) Altered pharmacokinetic parameters

(a) Pharmacokinetics is defined as the action of the body in response to a drug (Grogan & Preuss, 2021).

(b) Pharmacokinetic resistance is a concept that describes the body-related factors that alter a drug's effectiveness so that it does not reach its target or accomplish its intended goal. Pharmacokinetic resistance is universal to all drug therapy. The following factors can affect pharmacokinetic resistance (Grogan & Preuss, 2021):

- i. Absorption: Orally ingested agents for cancer can be affected by the presence or absence of food in the patient's stomach and permeability glycoprotein, or P-glycoprotein, which is found along the gastrointestinal tract. P-glycoprotein has been shown to reduce the oral bioavailability of some anticancer drugs.
- ii. Distribution: A higher volume of distribution means more drug penetrates into a tissue while it is more diluted in the plasma. The volume of distribution can be affected by gender, weight, plasma proteins, and circadian rhythm.
- iii. Metabolism: Cytochrome P450 enzymes are responsible for drug metabolism. Overexpression might lead to resistance due to the rapid inactivation of the drug.
- iv. Excretion of drugs: The kidney is the primary organ where

drugs are excreted. Changes in the glomerular filtration rate based on gender and ethnic differences can directly affect drug availability.

- (c) Coadministration of drugs might result in antagonism such that one drug may counteract or neutralize another. A common example is

tamoxifen, which needs to be converted to its active form by the metabolizing enzyme CYP2D6. This same enzyme is inhibited by specific selective serotonin reuptake inhibitors, thus reducing the efficacy of tamoxifen (Wang et al., 2019).

- (d) In some conditions, temporary resistance may be reversed by altering

**TABLE 4-6.** Performance Status Scales

| Scale                                                                                                                  | Grade/Score | Description                                                                                                  |
|------------------------------------------------------------------------------------------------------------------------|-------------|--------------------------------------------------------------------------------------------------------------|
| Eastern Cooperative Oncology Group (also known as ECOG, Zubrod, or World Health Organization) Performance Status Scale | 0           | Fully active; no performance restrictions                                                                    |
|                                                                                                                        | 1           | Strenuous physical activity restricted; fully ambulatory and able to carry out light work                    |
|                                                                                                                        | 2           | Capable of all self-care but unable to carry out any work activities; up and about > 50% of waking hours     |
|                                                                                                                        | 3           | Capable of only limited self-care; confined to bed or chair > 50% of waking hours                            |
|                                                                                                                        | 4           | Completely disabled; cannot carry out any self-care; totally confined to bed or chair                        |
|                                                                                                                        | 5           | Dead                                                                                                         |
| Karnofsky Performance Status Scale                                                                                     | 100         | Normal; no complaints; no evidence of disease                                                                |
|                                                                                                                        | 90          | Able to carry on normal activity; minor signs or symptoms of disease                                         |
|                                                                                                                        | 80          | Normal activity with effort; some signs or symptoms of disease                                               |
|                                                                                                                        | 70          | Cares for self; unable to carry on normal activity or do active work                                         |
|                                                                                                                        | 60          | Requires occasional assistance but able to care for most needs                                               |
|                                                                                                                        | 50          | Requires considerable assistance and frequent medical care                                                   |
|                                                                                                                        | 40          | Disabled; requires special care and assistance                                                               |
|                                                                                                                        | 30          | Severely disabled; hospitalization indicated although death not imminent                                     |
|                                                                                                                        | 20          | Hospitalization necessary; very sick; active supportive treatment necessary                                  |
|                                                                                                                        | 10          | Moribund; fatal processes progressing rapidly                                                                |
|                                                                                                                        | 0           | Dead                                                                                                         |
| Lansky Play-Performance Scale for Pediatric Patients                                                                   | 100         | Fully active; normal                                                                                         |
|                                                                                                                        | 90          | Minor restrictions with strenuous physical activity                                                          |
|                                                                                                                        | 80          | Active, but gets tired more quickly                                                                          |
|                                                                                                                        | 70          | Both greater restriction of and less time spent in active play                                               |
|                                                                                                                        | 60          | Up and around but minimal active play; keeps busy with quieter activities                                    |
|                                                                                                                        | 50          | Lying around much of the day but gets dressed; no active play; participates in all quiet play and activities |
|                                                                                                                        | 40          | Mostly stays in bed; participates in quiet activities                                                        |
|                                                                                                                        | 30          | Stuck in bed; needs help even for quiet play                                                                 |
|                                                                                                                        | 20          | Often sleeping; play is entirely limited to very passive activities                                          |
|                                                                                                                        | 10          | Does not play or get out of bed                                                                              |
|                                                                                                                        | 0           | Unresponsive                                                                                                 |

Note. Based on information from ECOG-ACRIN Cancer Research Group, n.d.; Lansky et al., 1987.



- drug delivery, dose, or scheduling of drug administration (Tortorice, 2018).
- b) Cancer cells develop resistance to antineoplastic agents via several mechanisms and pathways (Pan et al., 2016).
- (1) Primary or intrinsic resistance exists before patients receive treatment (Wang et al., 2019).
    - (a) Preexisting genomic alterations in some tumors may result in decreased responsiveness of cancer cells, such as triple-negative breast cancer, to chemotherapy and targeted agents (Wang et al., 2019).
    - (b) Tumor heterogeneity refers to the differences between tumors of the same type in different patients and the diverse genomic variation of the cancer cells within a tumor. Heterogeneity increases the risk for primary or secondary resistance. As cells divide, new variants emerge. With successive alterations, new driver variants continue to evolve, causing cancer cells to become resistant (Pan et al., 2016; Wang et al., 2019).
  - (2) Secondary or acquired resistance develops after exposure to the cytotoxic drug. Tumors initially respond to treatment, but genomic alterations and adaptive responses allow cancer cells to evade drug therapy (Pan et al., 2016; Vasan et al., 2019).
- c) Multidrug resistance is observed when tumor cells develop mechanisms to protect themselves against cytotoxic drugs (Tortorice, 2018).
- (1) Drug inactivation: Many cancer drugs must undergo metabolic activation to acquire clinical efficacy. However, cancer cells can develop resistance through decreased drug activation (Mansoori et al., 2017).
  - (2) Drug target alteration: A drug's efficacy is influenced by its molecular target and alterations of this target. In cancers, a second alteration in the target protein or changes in expression level due to epigenetic forces can ultimately lead to drug resistance (Wang et al., 2019).
  - (3) Drug efflux: This process involves reducing drug accumulation by removing the drug inside the cancer cell. Members of the adenosine triphosphate-binding cassette (ABC) transporter family include proteins that can stop drugs from entering a cell or remove them once they have entered (Vasan et al., 2019).
- (4) DNA reparability: Following chemotherapy-induced DNA damage, DNA repair pathways are activated in response to restoring the damage, leading to decreased efficacy (Vasan et al., 2019).
- (5) Inhibition of apoptosis
- (a) Tumor suppressor protein p53 (TP53) is a regulator protein that allows cells with undamaged DNA to proceed into the cell cycle. Following exposure to the DNA-damaging agents of cytotoxic therapy, an intact *TP53* gene prevents the tumor cell from entering the cell cycle, leading to apoptosis and decreased efficacy (Tortorice, 2018).
  - (b) Variants in the *TP53* gene are among the most common genetic changes observed in tumor cells and may occur in at least 50% of all tumors. When *TP53* function is lost, damaged cells can proliferate and transfer altered DNA to the next generations (Hientz et al., 2017). This leads to unregulated cellular proliferation; thus, the *TP53* variant usually indicates a poorer prognosis (Tortorice, 2018).
- (6) Changes to the tumor microenvironment: Tumors are composed of cells (e.g., immune and inflammatory cells), blood vessels, and an extracellular matrix, which respond uniquely to DNA-damaging treatment. The diversity of these responses adds to the cancer cell's ability to adapt to chemotherapy or targeted therapy (Wang et al., 2019).
- d) Poor adherence to cancer treatment, especially oral agents, includes misuse, overuse, and underuse. Lack of adherence negatively affects a provider's ability to determine treatment efficacy and effectiveness, contributes to increased healthcare costs, and can worsen disease and decrease overall patient survival (Atkinson et al., 2016).

## I. Adherence

1. Biomarker testing has revolutionized cancer treatment. As small molecule treatments are developed to target identified alterations, more patients are taking cancer treatment by mouth, either as a single agent or in combination with an immunotherapy or chemotherapy regimen.

2. Administration of oral anticancer medications (OAMs) in the home setting can provide convenience and enhanced quality of life (Huff, 2020; Murphy et al., 2019).
  - a) Fewer office visits
  - b) Less disruption of work and family life
  - c) Decreased patient travel
  - d) Ease of administration, including potentially less need for IV access
3. Challenges with the increased use of OAMs
  - a) Access concerns
    - (1) Financial burden
    - (2) Treatment delays due to prior authorization of financial coverage
    - (3) Drug procurement, including coordination with mail order or specialty pharmacies
  - b) Patient and caregiver safety due to exposure to hazardous medication or body fluids
  - c) Adherence concerns (Muluneh et al., 2018)
    - (1) Difficulty understanding label directions
    - (2) Misunderstanding the timing of the drug with food
    - (3) Discontinuing medication without informing the provider
  - d) Patient and caregiver knowledge of how to manage side effects
  - e) Lack of direct monitoring for adherence and toxicities (Murphy et al., 2019)
  - f) Patient population: Minority and uninsured patients may be negatively affected by oral oncolytic regimens because of a lack of access and adherence to medication regimens. Complex dosing, inability to identify and report toxicities, and insufficient funds to pay for treatment may affect adherence (Murphy et al., 2019).
4. Adherence is defined as the extent a patient's behavior conforms with the provider's recommendations about day-to-day treatment concerning timing, dosing, and frequency (Neuss et al., 2016).
  - a) Adherence to therapy is correlated with treatment success.
  - b) Nonadherence to the prescribed therapy can significantly affect outcomes (Krikorian et al., 2019; Morgan et al., 2017).
    - (1) Treatment failure and disease progression
    - (2) Increased toxicities and adverse drug events
    - (3) Increased healthcare costs
      - (a) Increased emergency department visits
      - (b) Unnecessary hospitalizations
      - (c) Additional diagnostic tests
      - (d) Additional prescriptions

5. Factors affecting the patient's ability to adhere to the prescribed medication regimen are multilayered, complex, and often occur simultaneously. These factors can generally be categorized into the following dimensions (Bryant et al., 2020; Dillmon et al., 2020; Goulart et al., 2021; Krikorian et al., 2019; Muluneh et al., 2018; Rosenberg et al., 2020; Washburn & Thompson, 2020; see Table 4-7):
  - a) Personal and patient
  - b) Medication and treatment
  - c) Healthcare system

**TABLE 4-7. Factors Influencing Adherence**

| Dimension                | Influencing Factors                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|--------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Personal and patient     | Age<br>Alcohol or drug abuse<br>Comorbid conditions<br>Competing life demands<br>Educational level<br>Emotional state: anxiety, depression, or distress<br>Expectations of the treatment results<br>Fatigue<br>Forgetfulness<br>Health beliefs<br>Health literacy: general lack of knowledge<br>Language barriers<br>Lifestyle: patient ability to incorporate regimen into a daily routine<br>Mental status or impaired cognition<br>Social support system<br>Socioeconomic status<br>Vision impairment |
| Medication and treatment | Complexity of regimen<br>Cost<br>Duration of treatment<br>Drug–drug and drug–food interactions<br>Fragmentation of care coordination with mail-order specialty pharmacies<br>Frequency of refills<br>Immediacy and evidence of benefit<br>Pill burden and number of pills<br>Size of pills<br>Side effects<br>Timing of administration related to food intake                                                                                                                                            |
| Healthcare system        | Access delays<br>Communication practices<br>Convenience of clinics<br>Coordination challenges with insurance-driven mail-order pharmacies<br>Cost and insurance coverage<br>Education provided prior to treatment<br>Relationship with providers<br>Satisfaction with care                                                                                                                                                                                                                               |

*Note.* Based on information from Bryant et al., 2020; Dillmon et al., 2020; Goulart et al., 2021; Krikorian et al., 2019; Muluneh et al., 2018; Rosenberg et al., 2020; Washburn & Thompson, 2020.

## 6. Strategies to promote adherence to OAM

## a) Factors that correlate with improved adherence include the following (Morgan et al., 2017; Muluneh et al., 2018; Rosenberg et al., 2020):

- (1) Favorable perception by the patient about the advantages of adhering to the medication
- (2) Higher levels of patient self-advocacy
- (3) Access to the drug
- (4) Comprehensive drug education
- (5) Patient and caregiver knowledge about diagnosis and treatment
- (6) Timely management of adverse effects
- (7) Frequency of follow-up

## b) Pretreatment assessment

- (1) Early identification of warning signs of barriers to adherence may help improve outcomes, reduce healthcare costs, and meet regulatory value-based expectations (Washburn & Thompson, 2020).
- (2) American Society of Clinical Oncology and Oncology Nursing Society standards state that prior to patients beginning a new chemotherapy regimen, a comprehensive assessment is completed, including medical history, physical examination, psychosocial assessment, and patient and caregiver comprehension of the disease and treatment plan (Neuss et al., 2016).

## c) Education

- (1) Initial and ongoing education is essential to assisting patients in safely managing OAM in the home setting.
- (2) Education-focused interventions for chronic disease management have demonstrated improvements in adherence, disease-specific knowledge, and symptom burden (Murphy et al., 2019).
- (3) Prior to beginning therapy with an OAM, patients and their families or caregivers should receive comprehensive education about the medications to be prescribed, including the following (Neuss et al., 2016):
  - (a) Drugs to be administered, as well as the schedule and duration of treatment
  - (b) Short- and long-term side effects of treatment, including instructions on when to discontinue the drug or contact healthcare providers
  - (c) Possible drug–drug and drug–food interactions
  - (d) The plan for missed doses

(e) Safe storage and handling of the OAM in the home, including how to manage unused medication

(f) Safe handling of body secretions and waste in the home

(g) Plans for follow-up, including laboratory tests and provider visits

- (4) Oral Chemotherapy Education sheets ([www.oralchemoedsheets.com](http://www.oralchemoedsheets.com)) were developed by the National Community Oncology Dispensing Association, Hematology/Oncology Pharmacy Association, Association of Community Cancer Centers, and Oncology Nursing Society. They include education about the drug, administration, side effects, and safety. These patient education sheets can be individualized with clinic or pharmacy phone numbers and information on when to return to the clinic for laboratory or other monitoring.

d) Nurses are in an ideal position to provide resources and recommendations to meet the learning needs of each individual and provide suggestions to promote adherence. Interventions should be tailored to the needs of the patient by addressing identified barriers (Rosenberg et al., 2020; Washburn & Thompson, 2020).

- (1) Multi-intervention strategies promote patient adherence by helping the patient overcome the numerous challenges associated with medication access, understanding how to take medications, and managing side effects. Providing ongoing education and support can improve quality care and safe administration of OAMs in the outpatient setting (Dillmon et al., 2020).
- (2) Suggestions and tools to promote adherence (Bryant et al., 2020; Krikorian et al., 2019; Rosenberg et al., 2020)
  - (a) Educate patients on the importance of self-advocacy and adhering to therapy.
  - (b) Encourage a daily routine for OAM dosing.
  - (c) Involve the assistance of other family members and friends.
  - (d) Provide calendars and recommend diaries with daily medication checklists.
  - (e) Recommend pillboxes as permitted by each OAM storage recommendation.

- (f) Use electronic reminders.
      - i. Smartphone applications
      - ii. Electronic alarms
      - iii. Pill bottles with built-in timers on the cap
      - iv. Text messaging
      - v. Electronic patient portal
    - (g) Follow up with phone calls. Evidence suggests that oncology nurses can help minimize the severity of symptoms with timely intervention, thus preventing nonurgent or preventable use of health services (Davis et al., 2020).
- 7. Adherence assessment and monitoring
  - a) Criteria for assessing adherence to an oral chemotherapy treatment plan (Neuss et al., 2016)
    - (1) Confirmation that the patient filled the prescription as written
    - (2) Inquiry regarding concerns about treatment costs
    - (3) Verification that the patient understands how to take the OAM as prescribed
    - (4) Verification that the patient understands what to do in case of missed doses
    - (5) Assessment for potential toxicity during each clinical encounter and in phone encounters: Adverse effects remain one of the leading causes of nonadherence to oral oncolytics (Salgado et al., 2017).
  - b) Methods of adherence monitoring
    - (1) There are several ways to assess medication adherence, but no current standard exists. Patient-reported adherence is considered one of the most accurate measures of adherence, and consistent use of a patient-reported outcome tool may be beneficial in oral oncolytic therapy (Morgan et al., 2017; Nachar et al., 2019).
    - (2) Adherence assessment (Michigan Oncology Quality Consortium, n.d.)
      - (a) Ask open-ended questions.
      - (b) Inquire regarding the patient's ability to take the medication and their ability to swallow and open the bottle, container, or package.
        - i. Do you have difficulty swallowing any of your medication?
        - ii. Do you have any difficulty opening pill bottles or packaging?
- iii. How are you taking your medication?
    - iv. What causes you to miss your doses?
    - v. How comfortable are you in managing the side effects of your medication?
  - (c) Assess symptom burden and patient and caregiver confidence in managing symptoms.
- 8. Interprofessional approach to patient support
  - a) Studies have shown that an interprofessional approach is needed to ensure adherence to OAMs to optimize outcomes (Morgan et al., 2017).
  - b) A comprehensive oral chemotherapy program includes support from the entire interprofessional healthcare team.
    - (1) Physician or prescriber
    - (2) Advanced practice provider
    - (3) Oncology registered nurse, including a clinical nurse or phone triage nurse
    - (4) Financial advocate
    - (5) Clinical pharmacist
    - (6) Specialty pharmacist
    - (7) Oral oncology nurse navigator or patient navigator
    - (8) Social worker
    - (9) Patient and caregiver
  - c) Practice considerations
    - (1) Address clinical gaps and identify the role of each stakeholder.
    - (2) Define the communication strategy, preferably within a secure electronic health record.
    - (3) Enter medication and patient care orders into an electronic health record.
    - (4) Build treatment plans individualized to each medication. For example, the National Community Oncology Dispensing Association (n.d.) Positive Quality Interventions are peer-reviewed clinical guidance documents for healthcare providers and may serve as a drug therapy management resource.
    - (5) Provide a communication plan to staff.
    - (6) Develop a robust education program.
    - (7) Obtain patient informed consent.
    - (8) Designate a navigator to facilitate care coordination within the interprofessional team.
    - (9) All stakeholders document all interventions and clinical encounters.
    - (10) Collaborate with the specialty pharmacy through proactive communication.

- (11) Collaborate with the financial advocate.
  - (a) Screen patients at high risk for financial toxicity.
  - (b) Obtain preauthorization for insurance reimbursement.
  - (c) Communicate denials to the health-care provider and coordinate the appeal process.
  - (d) Enroll patients in assistance programs.
    - i. A manufacturer co-pay card may be available for brand-name medications with commercial insurance.
    - ii. Medicare Part D
      - Foundation co-pay assistance grants
      - Manufacturer patient assistance programs
      - Low-Income Subsidy (Extra Help) (Centers for Medicare and Medicaid Services, 2021) to help patients with Medicare pay for prescription drugs; strict income limits to qualify
- d) Patient monitoring and follow-up
  - (1) Schedule laboratory, other monitoring (e.g., electrocardiogram), and provider follow-up visits that coordinate with the date the patient started taking the OAM.
  - (2) Conduct follow-up telephone calls to promote adherence, assess toxicity concerns, and provide reeducation and support.
  - (3) Consider other electronic means of communication through patient portals.
  - (4) Perform medication reconciliation, adherence, and toxicity assessments at each office visit (Neuss et al., 2016).
  - (5) Document oral chemotherapy follow-up using standardized forms or flow sheets (Anderson & Bettencourt, 2020).
- e) Tracking tools developed in spreadsheet format effectively track touchpoints and facilitate interprofessional coordination of care (Anderson et al., 2019; Ferguson et al., 2019). Common components to include in a tracking tool are included in Figure 4-2.
- f) Staff development
  - (1) Develop policies and procedures.
  - (2) Designate an educator for staff.
  - (3) Create checklists for staff to remind them of key elements required for education.
  - (4) Ensure education materials are current and comprehensive.

**FIGURE 4-2.** Elements of Oral Anticancer Medication Tracking

- 
- Patient name or identifier
  - Provider
  - Medication name
  - Date of prescription or order
  - Education date
  - Informed consent completed
  - Results of pharmacy benefit investigation, including prior authorization dates and patient co-pay or out-of-pocket expenses
  - Financial or co-pay assistance obtained
  - Dispensing pharmacy
  - Medication start date
  - Monitoring and provider follow-up visits scheduled
  - Dates for planned outreach calls
  - Refill due date
- 

Note. Based on information from Anderson et al., 2019; Ferguson et al., 2019.

- g) Develop quality outcomes for measuring performance and evaluate the use, adherence, and effectiveness of the policies, procedures, and checklists.

#### J. Toxicity grading and documentation

1. *Common Terminology Criteria for Adverse Events* (CTCAE) is used for adverse event reporting and has become widely accepted throughout the oncology community as the standard classification and severity grading scale for adverse events caused by antineoplastic therapy (NCI Cancer Therapy Evaluation Program, 2017). It is commonly used in clinical trials and daily nursing practice, as drug package inserts frequently recommend dose reductions based on CTCAE toxicity grading.
  - a) NCI Cancer Therapy Evaluation Program released version 5.0 in November 2017. Version 6.0 is still under development at the time of this writing. To access the document, visit [https://ctep.cancer.gov/protocoldevelopment/electronic\\_applications/docs/ctcae\\_v5\\_quick\\_reference\\_5x7.pdf](https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf).
  - b) An adverse event is defined as “any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure” (NCI Cancer Therapy Evaluation Program, 2017, p. 2).
  - c) The criteria incorporated into this toxicity grading scale are used to manage antineoplastic administration and dosing and in clinical trials to provide standardization and consistency in the definition of treatment-related toxicity (NCI Cancer Therapy Evaluation Program, 2017).



- d) In clinical trials, the grading system is designed to integrate into information networks for safety data exchange and influence data management for adverse event data collection, analysis, and patient outcomes associated with cancer research and care.
  - e) Grade refers to the severity of the adverse event. CTCAE displays grades 1–5 with unique clinical descriptions of severity for each adverse event based on the general guidelines listed in Table 4-8.
2. A patient-reported outcomes measurement system has been created as a companion to the CTCAE grading system. It considers the patient's perspective on adverse events that may be underdetected using the existing CTCAE system (NCI, 2022).
- a) Patient-reported outcomes are any report of the status of a patient's health condition that comes directly from the patient without interpretation by the clinician (Pirschel, 2017).
  - b) The MD Anderson Symptom Inventory is one patient-reported outcomes assessment tool and is

used to assess the severity and effect on daily living of 13 high-frequency or severity symptoms: pain, fatigue, nausea, disturbed sleep, distress, shortness of breath, difficulty remembering, lack of appetite, drowsiness, dry mouth, sadness, vomiting, and numbness and tingling (Cleeland, 2016).

- c) Any agent-specific symptoms (e.g., vincristine and peripheral neuropathy, methotrexate and stomatitis) should be assessed.

**TABLE 4-8.** Common Terminology Criteria for Adverse Events Grading System

| Grade | Severity         | Definition                                                                                                                                                                                                                                                                |
|-------|------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1     | Mild             | Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.                                                                                                                                                                      |
| 2     | Moderate         | Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL) (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money).                                            |
| 3     | Severe           | Medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (e.g., bathing, dressing, undressing, feeding self, using the toilet, taking medications, and not bedridden). |
| 4     | Life threatening | Life-threatening consequences; urgent intervention indicated.                                                                                                                                                                                                             |
| 5     | Death            | Fatality occurs related to the adverse event.                                                                                                                                                                                                                             |

Note. From *Common Terminology Criteria for Adverse Events* [v.5.0], by National Cancer Institute Cancer Therapy Evaluation Program, 2017 ([https://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/docs/CTCAE\\_v5\\_Quick\\_Reference\\_5x7.pdf](https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf)). In the public domain.

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# CHAPTER 5

## Clinical Trials and Drug Development

### A. Clinical research

1. Clinical research involves studies conducted on human beings to develop knowledge about human health and illness. These studies may include individuals or groups or use data or materials from humans (i.e., biospecimens).
2. Types of clinical research (U.S. Food and Drug Administration [FDA], 2018e)
  - a) Patient-oriented research includes individuals, data, or biospecimens to study.
    - (1) Mechanisms of human disease
    - (2) Treatments or interventions for disease
    - (3) Development of technology related to disease
  - b) Epidemiologic and behavioral research studies the distribution of disease, the factors that affect health, and how people make health-related decisions.
  - c) Health services research identifies the most effective ways to organize, finance, manage, and deliver high-quality care, reduce medical errors, and improve patient safety.
  - d) Outcomes research identifies healthcare practices and interventions to support more informed patient care decisions.
3. Clinical trials
  - a) A clinical trial is a type of patient-oriented research in which the patient (i.e., research participant) is prospectively assigned to an intervention to evaluate the effects of the intervention on health-related biomedical or behavioral outcomes (National Institutes of Health, 2017). Table 5-1 summarizes five types of clinical trials (Lin, 2020; National Cancer Institute, 2020; Ness & Royce, 2017; Stoney & Johnson, 2018; U.S. FDA, 2018e).
  - b) Cancer clinical trials are essential for identifying new, more effective therapies to improve disease prevention, detection, treatment, and rehabilitation.
    - (1) Clinical trials have had a significant role in improving outcomes for people with cancer.

**TABLE 5-1.** Types of Clinical Trials

| Type of Trial   | Description                                                                                                                                                                                                                                                                                                                                                                                        |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Prevention      | Evaluate the effectiveness of ways to reduce the risk of developing a disease or preventing a disease from returning by one of the following: <ul style="list-style-type: none"> <li>• "Doing" something (e.g., lifestyle changes, including diet, exercise, or smoking cessation)</li> <li>• "Taking" something (e.g., medications, vitamins, vaccines)</li> </ul>                                |
| Diagnostic      | Develop better tests or procedures to more accurately identify and diagnose a disease or condition (e.g., imaging tests, laboratory tests, biomarkers).                                                                                                                                                                                                                                            |
| Screening       | Assess new or better ways of detecting disease or health conditions earlier in healthy people. Examples include obtaining the following: <ul style="list-style-type: none"> <li>• Tissue samples</li> <li>• Laboratory tests, including genetic testing</li> <li>• Imaging tests</li> <li>• Physical examinations</li> <li>• Health histories, including family histories and pedigrees</li> </ul> |
| Quality of life | Evaluate measures to improve comfort and quality of life for people with chronic illnesses through better therapies or psychosocial interventions. <ul style="list-style-type: none"> <li>• Focus can be on the patient, families, or other caregivers.</li> <li>• These are also known as supportive care trials.</li> </ul>                                                                      |
| Treatment       | Test new treatments or devices, new combinations of drugs, or new approaches to surgery or radiation therapy. Treatment trials, especially trials for drugs that are not yet approved for general use (i.e., investigational drugs), are categorized by phases.                                                                                                                                    |

*Note.* Based on information from National Cancer Institute, 2020; Ness & Royce, 2017.



- (2) For example, results from breast cancer clinical trials have led to lengthened survival and improvements in screening, surgery, chemotherapy, radiation therapy, and hormone therapy.
  - c) Ideas for clinical trials are generated from clinical and basic sciences.
    - (1) Many ideas come from basic science research, which increases understanding of cancer biology. These ideas are first investigated in the laboratory. Treatments with the most promising results are studied in clinical trials.
    - (2) Some ideas come from the results of previous clinical research because new questions are often raised as previous ones are answered.
    - (3) Ideas for clinical trials also may come from patients and healthcare providers as they try to determine how to manage a disease and its side effects.
  - d) Patients choose to participate in clinical trials for different reasons. These reasons will depend on their beliefs, culture, disease status, treatment options, and knowledge and perception about clinical trials.
    - (1) Understanding an individual's reasons for participating in a clinical trial will help oncology nurses know how to best support them.
    - (2) Common reasons for patient participation in clinical trials (Anderson et al., 2018)
      - (a) Access to treatments that may not otherwise be affordable
      - (b) Hope that they will be given better treatment in the trial than the current standard
      - (c) Desire to contribute to research and advance science so that others may benefit in the future
      - (d) A lack of available treatment options
4. Clinical trial enrollment
- a) Validity
    - (1) The validity of clinic trial results partially depends on recruiting and enrolling adequate numbers of the required participant population.
    - (2) Approximately 20% of adult patients with cancer are eligible for a clinical trial, but only 2%–8% participate in a cancer clinical trial (Unger et al., 2021).
    - (3) Table 5-2 provides a snapshot of patient-specific barriers and the strategies that can be used to overcome them.
  - b) Barriers
    - (1) Restrictive eligibility criteria are barriers to enrolling patients in clinical trials.
      - (a) The American Society of Clinical Oncology and Friends of Cancer Research collaborated on a joint project to evaluate current eligibility criteria and determine how to broaden the criteria (Kim et al., 2017).
      - (b) The initial recommendations from the collaboration were to ease eligibility criteria without compromising safety. This resulted in FDA adopting the recommendations into guidance documents for patients with brain metastases, HIV/AIDS, organ dysfunction, prior and concurrent malignancies, and minimum age considerations for inclusion of pediatric patients.
      - (c) A second set of recommendations address broadening criteria related to washout periods and concomitant medications, performance status, laboratory test intervals and reference ranges, and prior therapies (Kim et al., 2021).
    - (2) Another barrier to enrollment includes provider lack of knowledge about clinical trials.
      - (a) Oncology nurses need to learn about clinical trials to help answer patient questions and dispel myths.
      - (b) Resources to help nurses and patients learn more about clinical trials include the following:
        - i. American Cancer Society Treatment and Support ([www.cancer.org/treatment.html](http://www.cancer.org/treatment.html))
        - ii. Cancer.Net ([www.cancer.net](http://www.cancer.net))
        - iii. Center for Information and Study on Clinical Research Participation Education Center ([www.cisrpf.org/education-center](http://www.cisrpf.org/education-center))
        - iv. National Cancer Institute Cancer Information Service ([www.cancer.gov/contact](http://www.cancer.gov/contact))
        - v. National Cancer Institute Clinical Trials Information for Patients and Caregivers ([www.cancer.gov/about-cancer/treatment/clinical-trials](http://www.cancer.gov/about-cancer/treatment/clinical-trials))
5. The protocol
- a) The written protocol is the heart of any research project; it serves as a recipe to ensure that the

**TABLE 5-2.** Patient Barriers to Recruitment in Clinical Trials

| Barrier Category                                                                                                                                                                     | Examples of Barriers                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Examples of Strategies                                                                                                                                                                                                                                                                                                                                                                                                   |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| General patient population                                                                                                                                                           | Lack of awareness or understanding about clinical trials<br>Lack of trust in research and the medical community<br>Demands of the study (e.g., frequent visits)<br>Fear of being a guinea pig<br>Concerns about side effects<br>Research site not being close to home<br>Costs and financial burden                                                                                                                                                                             | Introduce clinical research or trials earlier within the patient experience.<br>Use the electronic health record to trigger an alert if a patient is likely eligible for an ongoing clinical trial.<br>Involve members of the study population in planning efforts when possible.                                                                                                                                        |
| Underserved or under-represented patient populations, including older adults, racially or ethnically diverse groups, LGBTQ+ population, and patients with well-managed comorbidities | Lack of awareness of clinical trials<br>Lack of awareness of benefits to participation<br>Sense that participants do not get anything from participation<br>Distrust of doctors<br>Different values or beliefs<br>Lack of cultural sensitivity<br>Language or literacy barriers<br>Employment obligations<br>Comorbid conditions<br>Presentation at late stage of disease when trial may not be available<br>Limited transportation<br>Lack of minority principal investigators | Increase awareness in the community.<br>Bring clinical trials to the intended study population.<br>Invest in community education and outreach programs.<br>Enhance credibility of the study by using a community spokesperson or layperson outreach worker.<br>Dispel myths about clinical trials.<br>Provide culture- and language-appropriate informational materials.<br>Involve minority researchers and physicians. |

Note. Based on information from Anderson et al., 2018; Nipp et al., 2019; Niranjana et al., 2021; Vuong et al., 2020.

activities outlined in the study to answer scientific questions are performed in a consistent and repeatable manner.

- b) The protocol is written by a team that includes physicians, scientists, statisticians, nurses, and others (e.g., pharmacists).
- c) Every protocol should include the same parts, but the order may differ.
- d) The basic elements of a protocol are listed in Figure 5-1 (Bartrum & Karp, 2018; International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, 2016; Ness & Royce, 2017).

- (1) The information included in a clinical trial protocol is used to write study-related orders, such as tests, procedures, and medications to be administered.
- (2) It also should include instructions on when to contact a research team member.
- (3) The protocol can also provide helpful information about the following:
  - (a) Potential or anticipated side effects or adverse events of the intervention and how to treat them
  - (b) Administration instructions
    - i. Rate of infusion for study medication
    - ii. Pre- and postmedication or hydration needs

- iii. How to treat side effects, including when to hold or reduce dosage of study medication

- (c) Safety assessments, including blood work and physical examinations
- (d) When biospecimens are to be collected
- (e) Randomization procedures

#### 6. Protecting research participants

- a) Good clinical practice in conducting research refers to a standard that ensures ethical and scientific quality in research with human participants (i.e., living individuals who volunteer to participate in clinical research).
- b) Adherence to the principles of good clinical practice, including adequate participant protection, is universally recognized as a critical requirement for research involving human participants (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, 2016).
- c) Human participants comprise living individuals, their data, and biospecimens.
- d) Although several historical events highlight unethical conduct in clinical research, the Nuremberg trials and the National Research Act of 1974 have significantly impacted how clinical research is conducted and how participants are protected.



**FIGURE 5-1.** Basic Sections of a Protocol

- Title page—title of study, version date, local protocol number, name of investigator(s)
- Table of contents
- Abstract—summary of the study background, objectives, eligibility, and design
- Introduction—outlines the objectives and scientific support for the study
- Eligibility assessment and enrollment—describes the patients who can participate in the study
  - Inclusion criteria—criteria that a patient must meet to be eligible for the clinical trial
  - Exclusion criteria—reasons that a patient may not be eligible for the clinical trial
- Study implementation—provides information about the study treatment and plan
  - Study design or structure
  - Information about how the intervention will be given
  - Other information or specimens that will be collected
  - What other treatments a patient can or cannot receive while on the study
  - Reason the patient might be taken off the study
  - What needs to be done after the patient goes off the study
- Supportive care—how a patient's symptoms can be managed while the patient is on the study
- Data collection, evaluation, and reporting
  - What types of information about a patient need to be collected
  - How this information needs to be documented and evaluated
- Human subjects protection procedures, including consent and assent
- Drug information, including known or suspected side effects

*Note.* Based on information from Bartrum & Karp, 2018; International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, 2016; Ness & Royce, 2017.

- (1) Nuremberg trials
  - (a) The Nuremberg trials revealed horrific experimentation by Nazi doctors conducted on prisoners of German concentration camps during World War II.
  - (b) The knowledge of these atrocities led to the creation of 10 ethical principles for conducting clinical research outlined in the Nuremberg Code (<https://research.wayne.edu/irb/pdf/2-2-the-nuremberg-code.pdf>).
  - (c) These principles include voluntary consent of the individual to participate in research and their ability to withdraw that consent at any time; the need for animal experimentation before human experimentation; and the determination that the benefits outweigh the risks of participation to protect the individual from harm.
- (2) National Research Act of 1974 (National Commission for the Protection of Human

Subjects of Biomedical and Behavioral Research, 1979)

- (a) In 1974, U.S. Congress created the National Research Act, which codified human participant protection regulations.
  - (b) The act established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.
  - (c) This commission was charged with identifying basic ethical principles in conducting biomedical and behavioral research on human participants.
  - (d) This culminated in the Belmont Report, which delineated the difference between medical practice and research and outlined three ethical principles guiding human research—respect for persons, beneficence, and distributive justice.
  - (e) Table 5-3 summarizes these principles and how they are applied in clinical research.
- e) Regulations and guidance documents that affect the conduct of clinical trials are designed to protect patients participating in clinical research and ensure the accuracy of the data being collected. Several groups with regulatory authority are involved in clinical trials in the United States.
- (1) The Office for Human Research Protections maintains regulatory oversight and provides advice on ethical and regulatory issues in biomedical and behavioral research funded or supported by the U.S. Department of Health and Human Services.
  - (2) FDA has oversight for product development (e.g., drugs, biologics, devices) regardless of the funding source.
- f) Ethical review of the protocol
- (1) All clinical trials must have an ethical review and be approved by an institutional review board (IRB) prior to implementation (Institutional Review Boards, 2020; Protection of Human Subjects, 2018). If any changes happen in the protocol (i.e., protocol amendment), the IRB will also review the changes before implementation.
  - (2) The primary responsibility of the IRB is to protect the rights and safety of patients.
  - (3) The IRB must decide whether the anticipated benefit of new knowledge or

**TABLE 5-3.** Application of the Three Principles of the Belmont Report

| Principle                                                                                                                                                                                                 | Application                                                                                                                                                                                                                                                                          |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Respect for Persons</b> <ul style="list-style-type: none"> <li>• Individuals should be treated as autonomous agents.</li> <li>• People with diminished autonomy are entitled to protection.</li> </ul> | Participants must be given the opportunity to choose what shall or shall not happen to them.<br>The consent process must include three elements: <ul style="list-style-type: none"> <li>• Information sharing</li> <li>• Comprehension</li> <li>• Voluntary participation</li> </ul> |
| <b>Beneficence</b> <ul style="list-style-type: none"> <li>• Human participants should not be harmed.</li> <li>• Research should maximize possible benefits and minimize possible risks.</li> </ul>        | Assessment of risks and benefits should be performed by an investigator and an institutional review board.                                                                                                                                                                           |
| <b>Justice</b> <ul style="list-style-type: none"> <li>• The benefits and risks of research must be distributed fairly</li> </ul>                                                                          | Fair procedures and outcomes should be performed during selection of research participants.<br>Eligibility criteria should include those who may benefit and exclude those who may be harmed.                                                                                        |

Note. Based on information from National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979.

improved health in a clinical trial justifies the risks patients may experience.

- (4) The IRB cannot approve research where the risks are too high compared to the anticipated benefits.

g) Informed consent

- (1) Informed consent is an ongoing process of communication and understanding between a patient and investigator.
- (2) As a part of this process, the patient decides whether to agree to enter a clinical trial voluntarily.
- (3) The informed consent process includes sharing information about the nature of the research and evaluating the patient's comprehension of that information and their voluntary decision to participate (National Commission, 1979; Protection of Human Subjects, 2018, 2020).

(a) One tool used in this process is the informed consent document. Common information in this document is based on the federal regulations found in Figure 5-2 (Elements of Informed Consent, 2020; General Requirements for Informed Consent, 2018).

(b) The patient indicates initial agreement by signing an informed consent document. However, this does not mean that the patient must continue in the clinical trial if they decide to withdraw for any reason.

7. Roles and responsibilities: The clinical research enterprise is vast and involves many individuals and groups (Ness & Royce, 2017).

**FIGURE 5-2.** Common Elements of the Informed Consent Document

- Statement that the clinical trial involves research, including the following:
  - Explanation of the purpose of the research
  - Expected length of participation
  - Description of procedures to be followed
  - Identification of any procedures that are experimental
- Any predictable risks to patients, as well as a statement that the intervention or procedure may cause unforeseeable risks
- Any benefits to patients or others
- Any alternatives to study participation
- How patients' confidentiality will be maintained
- Contact people for questions related to research and the research participants' rights
- Statement that participation is voluntary and that there will be no penalty if patients do not want to participate
- Reason why investigators may stop treating patients on the clinical trial
- Costs for which patients may be responsible
- Whether patients will receive any compensation for participation in the clinical trial
- Statement that patients will be notified of new findings that may affect their decision to continue participation
- Statement about the use of or removal of personally identifiable information or identifiable biospecimens and use for future research or not
- For U.S. Food and Drug Administration–regulated applicable clinical trials: statement indicating that clinical trial information will be submitted for inclusion into a registry databank; specifically, the consent must read: "A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time" (General Requirements for Informed Consent, 2018, item c).

Note. Based on information from Elements of Informed Consent, 2020; General Requirements for Informed Consent, 2018.

a) Every clinical trial team will have a principal investigator responsible for the overall conduct of the clinical trial and the research participants. The team may also include the following:

- (1) Subinvestigators are selected by the principal investigator to provide support for the conduct of a clinical trial.
- (2) Study coordinators are responsible for organizing the day-to-day activities of a clinical trial at a specific site (e.g., gathering data).
- (3) Clinical data managers are responsible for organizing and collecting the data required by the protocol.

b) Nurses at all levels of education and practice play key roles in clinical research.

- (1) Nurse researchers provide leadership in clinical research development, performance, and analysis.
- (2) Clinical trial nurse
  - (a) Clinical trials nursing is a specialty nursing role that coordinates clinical trials and manages patients during those trials.
  - (b) Other titles for this role include clinical research nurse, clinical trials coordinator, and clinical research associate.
  - (c) Specific responsibilities and competencies for oncology clinical trial nurses have been developed by the Oncology Nursing Society (2016).
- (3) Direct care nurses are primarily responsible for the clinical care of patients. Their clinical trials responsibilities may include providing patient and caregiver education, finding information about clinical trials for patients, advocating for ethical care, administering treatments, collecting biospecimens, and monitoring for side effects (Parreco et al., 2012; see Table 5-4).

#### B. Drug and biologic development process

1. The development process is highly regulated and involves many steps to prove that a drug or biologic is safe and effective before being marketed. These steps can be divided into three main stages—discovery and preclinical testing, clinical testing, and FDA review (Buckley et al., 2020; U.S. FDA, 2018b; see Table 5-5).
2. The two essential roles for drug development in the United States are the sponsor and the FDA (Buckley et al., 2020).
  - a) Sponsor

- (1) The sponsor is responsible for developing the product (i.e., drug or biologic) and producing the evidence (i.e., safety and efficacy) to the FDA.

- (2) Most sponsors are pharmaceutical or biotechnology companies.

- (3) Other sponsors may include academic medical centers or the National Cancer Institute Cancer Therapy Evaluation Program.

b) FDA reviews the evidence against the standards of excellence (i.e., good clinical, manufacturing, and laboratory practice) to ensure that the product is safe and effective.

#### 3. Investigational New Drug (IND) application

a) Before beginning a clinical trial using a newly developed drug or biologic, the sponsor must submit an IND application to FDA (Investigational New Drug Application, 2020). This process protects clinical trial participants from unreasonable and significant risk.

b) Information included in the IND application

- (1) Animal study and toxicity data
- (2) Manufacturing information
- (3) Protocols for the clinical trials to be conducted
- (4) Information about the investigator

c) FDA review

- (1) The FDA has 30 days to review the initial IND application before clinical trials may begin.
- (2) If it finds any potential safety concerns (e.g., patients are exposed to unreasonable or significant risk; not enough information is provided about risk; the principal investigator is not qualified), the sponsor will need to resolve these concerns to FDA satisfaction.

d) The sponsor is responsible for informing the FDA about new protocols, amendments to existing protocols, and any serious side effects noted during the trials. This information continues until the sponsor files a marketing application or withdraws the IND.

e) The FDA assigns an IND number or a BB-IND number for biologic agents, often noted in the protocol (e.g., title page, pharmaceutical section).

#### 4. Conducting clinical trials

a) The FDA will notify the sponsor that the IND is safe to proceed, which means clinical trials may begin.

b) Clinical trials have three main phases, plus a fourth phase after a drug enters the market (Buckley et al., 2020; Investigational New Drug Application, 2020; see Table 5-6).

**TABLE 5-4.** Direct Care Nurse Responsibilities When Caring for a Clinical Trial Patient

| Research Activity                                  | Responsibilities                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|----------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Identifying which patients are on a clinical trial | Know how the organization identifies a patient on a clinical trial.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Maintaining the informed consent (IC) process      | <p>Locate the signed IC document. Ideally it should be in the patient's medical record, but the location depends on the organization's policy.</p> <p>Read the IC document to learn more about the clinical trial.</p> <p>Support the patient's decision to participate in the clinical trial. Encourage the patient to have others (e.g., family, referring physician) included in discussions about participation in a clinical trial. Encourage patient to read the IC document and other materials about the clinical trial and to ask questions.</p> <p>Assess the patient's comprehension of the study and his or her responsibilities by using open-ended questions.</p> <p>If asked to serve as a witness, know the organization's definition of witness (e.g., witness to the patient's signature or to the actual IC discussion).</p> <p>If unable to answer the patient's questions, contact the principal investigator or other designated member of the research team.</p> |
| Administering the study drug or intervention       | <p>Obtain a copy of the study protocol. Information about the study intervention is in either the study design or pharmaceutical section of the protocol. The medical orders should be consistent with the protocol.</p> <p>Determine if other medications or interventions are needed (e.g., specific hydration before or after chemotherapy administration).</p> <p>Understand the appropriate handling of the drug, including how soon an IV drug needs to be infused after it is mixed.</p> <p>For study medications that the patient will self-administer, reinforce the proper usage, storage, and disposal of the drug and what to do for a missed dose.</p>                                                                                                                                                                                                                                                                                                                     |
| Monitoring safety and response to intervention     | <p>The types of laboratory and/or imaging studies that will be used to monitor response to the study intervention should be listed in the protocol's study calendar.</p> <p>Assist in the identification of adverse events (AEs). An AE is similar to a side effect or toxicity except with these terms, a relationship to the intervention is implied. In research, the cause of the AE will be determined by the principal investigator and may or may not be related to the study intervention. Avoid asking questions about specific AEs that may be anticipated; these are found in the protocol and the IC document. Instead, ask the patient open-ended questions to help in the identification of AEs.</p> <p>Know when an AE should be reported to the research team and how to contact them.</p>                                                                                                                                                                              |
| Performing documentation and data collection       | <p>Document all prescription and over-the-counter medications, including complementary and alternative medications. Document the dose, how long the patient has been taking the medication, and the indication for its use.</p> <p>Document study-specific interventions. For IV study drugs, include the start and stop time.</p> <p>Document the AE details:</p> <ul style="list-style-type: none"> <li>• When the AE started</li> <li>• Description of the AE, which will be used by the research team to indicate its severity</li> <li>• Treatment for the AE</li> <li>• When the AE ended, if known</li> </ul> <p>For studies that require biospecimen collection, document the type of sample collected (e.g., blood, saliva), the time the sample was collected, how the sample is to be stored (e.g., room temperature, on ice), and whom to contact to pick up the specimen (e.g., research nurse, research assistant).</p>                                                   |

Note. Based on information from Parreco et al., 2012.

- c) The sponsor is responsible for ensuring that the clinical trials are monitored for patient safety and quality data.
5. The FDA review process starts with the sponsor applying to market a product. For drugs, this is called a new drug application (NDA), and for biologics, it is called a biologics license application (BLA) (Buckley et al., 2020; U.S. FDA, 2018b).

- a) The NDA or BLA should provide evidence of the product's safety and effectiveness, the appropriateness of the proposed labeling, and the consistent manufacturing of the drug.
- b) Clinical trial end points used by the FDA to assess effectiveness are based on tumor or symptom assessments (U.S. FDA, 2018a; see Table 5-7).

**TABLE 5-5.** Drug Development Process

| Drug Development Stage                                      | Description                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|-------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Discovery and preclinical testing                           | <p>Discovery includes finding a lead compound or a promising molecule that could become a drug by acting on a target to alter a disease. Sources of drugs include plants, animals, minerals, microbiology, semisynthetic or synthetic compounds, and recombinant DNA.</p> <p>Biologic products (e.g., monoclonal antibodies, vaccines, gene therapy) are made from living organisms and are larger molecules or a mixture of molecules.</p> <p>Completion of laboratory and animal testing to answer essential questions</p> <ul style="list-style-type: none"> <li>• Drug absorption, distribution, metabolism, and excretion</li> <li>• Potential benefits and mechanisms of action</li> <li>• Determination of the best dosage for a clinical trial</li> <li>• Side effects or adverse events (i.e., toxicity)</li> </ul> <p>Manufacturing of the drug</p> <ul style="list-style-type: none"> <li>• Preliminary stability of the drug</li> <li>• Finding the optimal drug formulation (e.g., oral or IV, additive needed)</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Clinical testing                                            | <p>Begins with the submission of the investigational new drug (IND) application</p> <p>Designing and conducting clinical trials to answer specific research questions</p> <p>Selecting investigators and research sites</p> <p>Monitoring the clinical trials for patient protection and quality data</p> <p>Sharing safety information with investigators</p> <p>Ensuring accountability for all investigational drug supplies</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| U.S. Food and Drug Administration (FDA) review for approval | <p>Begins with sponsor submission of the new drug application (NDA) or biologics license application (BLA) to FDA</p> <p>Full review by each NDA reviewer of their section of the application (e.g., medical officer and statistician review the clinical data)</p> <ul style="list-style-type: none"> <li>• Routine inspections of clinical study sites to verify accuracy of the clinical data submitted by the sponsor in the NDA and that no data have been withheld</li> <li>• Facilities where the drug will be manufactured</li> </ul> <p>Review of the drug's labeling (also known as the package insert) to ensure appropriate information is communicated to healthcare professionals and patients and assist sponsor in refining the prescribing information</p> <p>Granting of FDA approval</p> <p>Regulatory mechanisms to speed up the review and approval process for drugs that treat serious diseases</p> <ul style="list-style-type: none"> <li>• Priority review: FDA's goal is to act on the NDA within 6 months.</li> <li>• Breakthrough therapy: This process is designed to expedite the development and review of drugs that may demonstrate substantial improvement over available therapy.</li> <li>• Accelerated approval: This allows surrogate end points (e.g., a laboratory measurement, radiographic image, physical sign) to be used for drug approval to fill an unmet need.</li> <li>• Fast track: This method facilitates the development and expedited review of drugs.</li> </ul> |

Note. Based on information from Lin, 2020; National Cancer Institute, 2020; Ness & Royce, 2017; Stoney & Johnson, 2018; U.S. Food and Drug Administration, 2018b, 2018d.

c) FDA's Center for Drug Evaluation and Research or Center for Biologics Evaluation and Research will then review the application against its standards of excellence.

d) An FDA approval grants a license for interstate commerce.

- (1) A drug or biologic is not licensed without a use.
- (2) Each drug or biologic is approved for a specific use, also referred to as an indication.
- (3) A drug or biologic may have more than one indication.

e) The license and description of the safe and effective use of the product are stated in the approved package insert (product label).

f) When a drug or biologic is not used per the prescribing information or indication, this is considered an off-label use.

6. Postapproval: Information about a drug's safety continues to evolve even after FDA approval. Sponsors also may continue the development of the drug for other indications (U.S. FDA, 2018b).

a) FDA reviews reports of problems with all drugs and can decide if cautions need to be added to prescribing information.

- b) After the initial approval to market a drug, a sponsor may want to add other indications, change the formulation (e.g., IV to oral) or dosage strengths, or perform other labeling changes. This requires the submission of a supplement application to FDA for approval.
7. Drug names
- a) The naming of drugs is complex.
- (1) All pharmaceutical substances have three main names—the chemical name, the approved official or generic name, and the proprietary or brand name.
  - (2) Generic names will start with a lower-case letter, whereas the proprietary name begins with a capital letter.
  - (3) For patient safety, it is important to avoid naming a drug too similar to an existing drug name (Karet, 2019).
- b) The chemical name is issued by the International Union of Pure and Applied Chemistry.
- (1) The scientific name is based on the compound's chemical structure.
  - (2) This name is not used to identify the drug in clinical practice.
- c) A generic or nonpropriety name is given to the active drug ingredient.
- (1) The United States Adopted Name (USAN) program assigns the generic name.
  - (2) The assigning of the generic name is part of the drug development process because a drug cannot be marketed without it.
  - (3) This is the name used in clinical practice.
- d) Proprietary names are created by the company that patents the drug.
- (1) The name identifies the drug during the years that the company has exclusive rights to make, sell, and use the drug.
  - (2) Initially, an alphanumeric name may be used until a propriety or generic name is available.

**TABLE 5-6.** Phases of Clinical Trials

| Phase | Description                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|-------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1     | <p>Goal: Determine a dose or dosing schedule that is safe in humans—the maximum tolerated dose (MTD). Studies are small, usually 15–60 patients. Eligible patients may have a variety of cancers but have no available standard therapy options. All patients receive the study drug. Drug doses are increased slowly, and patients are monitored for side effects until the MTD is found. Phase 1 clinical trials help to determine the drug's pharmacokinetics, measuring how the drug is absorbed, distributed, metabolized, and excreted, revealing the following:</p> <ul style="list-style-type: none"> <li>• Drug dose</li> <li>• Administration schedule</li> <li>• Dose adjustments for certain medical conditions</li> <li>• Possible drug interactions</li> </ul>                                                                                                                                                                                                                                                                                             |
| 2     | <p>Goal: Evaluate the activity or effectiveness of the drug or regimen and determine if there should be further development of an intervention. Studies are larger in size (e.g., 100–300) and include patients for whom the current standard of care is not effective. In most phase 2 clinical trials, all patients receive the same intervention, including the same dose of the drug being studied (if it is a drug clinical trial). However, different trial designs exist (e.g., adaptive, Bayesian), in which patients may be randomized to one of several treatment groups.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 3     | <p>Goal: Compare a new drug or treatment to a current standard treatment. Studies include large numbers of patients (e.g., hundreds to thousands) and are conducted at many locations. The standard design for a phase 3 clinical trial is a randomized controlled trial, allowing comparison of a new intervention to the current standard of care. Patients on the clinical trial will be assigned to one of two or more groups:</p> <ul style="list-style-type: none"> <li>• The treatment group, receiving the new intervention</li> <li>• A control group, receiving either the standard of care or a placebo, if there is no treatment option</li> </ul> <p>To ensure study results are due to the intervention, researchers may use the following:</p> <ul style="list-style-type: none"> <li>• Randomization: Patients are assigned to the study groups with an equal chance of receiving each of the treatment options.</li> <li>• Masking or blinding: Patients and research team members do not know which intervention each patient is receiving.</li> </ul> |
| 4     | <p>Goal: Further evaluate risks, benefits, and uses in real-life scenarios. Phase 4 trials are follow-up investigations for a drug recently marketed to and available for use by the general public. Studies include very large numbers of patients (e.g., thousands).</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

Note. Based on information from Investigational New Drug Application, 2020; Stoney & Johnson, 2018; U.S. Food and Drug Administration, 2018b, 2018e.



**TABLE 5-7. End Points for Drug and Biologic Approval**

| End Point                              | Definition                                                                                                                                                                                                                                                                                                                    |
|----------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Based on Tumor Assessments</b>      |                                                                                                                                                                                                                                                                                                                               |
| Disease-free survival                  | Time from randomization until disease recurrence or death from any cause                                                                                                                                                                                                                                                      |
| Objective response rate                | Proportion of patients with reduction of tumor size of a predefined amount and for a minimum time period<br>Sum of partial responses plus complete responses<br>Measure from time of initial response until progression<br>Standardized criteria (e.g., Response Evaluation Criteria in Solid Tumors [RECIST]) when available |
| Progression-free survival              | Time from randomization until objective tumor progression or death                                                                                                                                                                                                                                                            |
| Time to progression                    | Time from randomization until objective tumor progression, excluding death                                                                                                                                                                                                                                                    |
| Time to treatment failure              | Composite end point from time of randomization to discontinuation of treatment for any reason (e.g., progressive disease, toxicity, death)                                                                                                                                                                                    |
| <b>Based on Symptom Assessments</b>    |                                                                                                                                                                                                                                                                                                                               |
| Symptom improvement or palliation      | Direct measure of clinical benefit rather than a surrogate end point                                                                                                                                                                                                                                                          |
| Time to progression of cancer symptoms | Direct measure of clinical benefit rather than a potential surrogate end point                                                                                                                                                                                                                                                |

Note. Based on information from U.S. Food and Drug Administration, 2018a.

- (3) The FDA reviews the proprietary name as part of the product labeling review for an NDA.

#### 8. Generic drugs

- Once a new drug is approved, the sponsor (i.e., the company manufacturing the drug) has exclusive rights to market the drug for a period. Other drug manufacturers may develop the drug once the patent and exclusive marketing rights have expired (U.S. FDA, 2018b).
- Generic drugs must have the same dosage, safety, strength, quality, mechanism of action, and prescribing information as the brand-name drug.
- Generic drug manufacturers conduct bioequivalence studies and file an abbreviated NDA. Bioequivalence studies include pharmacokinetic, pharmacodynamic, clinical, and in vitro studies.

#### 9. Biosimilars

- The FDA approves the originator biological product (reference product) through the traditional drug approval process, known as a stand-alone BLA.
  - An abbreviated biological licensure pathway can be used when a biological product is demonstrated to be highly similar to an existing FDA-licensed biological product.
  - These similar products are referred to as biosimilars. They have “no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency” (U.S. FDA, 2015, p. 3).
  - Biosimilars undergo a rigorous evaluation by the FDA (Declerck et al., 2017; Harvey, 2017; U.S. FDA, 2017).
- When naming a biologic product, the nonproprietary or proper name reflects scientific characteristics, such as chemical structure and pharmacologic properties.
  - The FDA designates the proper name in the license for the use of each product.
  - This name helps healthcare providers identify products and distinguish biological products from one another.
  - The proprietary name is the trademarked name (U.S. FDA, 2017).
- FDA’s naming convention for biologics consists of a core name (e.g., filgrastim, epoetin alfa) and an FDA-designated suffix.
  - The core name is designated by the USAN program.
  - This name will be the same for biosimilars.
  - The suffix is composed of four lower-case letters and signifies the originator of the product (e.g., replicamab-cznm, replicamab-hjxf).
  - The FDA may attach a prefix to distinguish a product under a different BLA prior to 2017 (e.g., ado-trastuzumab emtansine, trastuzumab).
  - These are important differences to understand to ensure patient safety (U.S. FDA, 2017).
- Biosimilars can be approved for fewer indications and conditions than the approved biologic reference product.
  - The labeling information for a biosimilar has more details comparing the biosimilar to the reference products.
  - Nurses and other healthcare providers should read the product labeling for uses,

routes of administration, and therapeutic profiles for each biosimilar agent (Buske et al., 2017; Harvey, 2017; U.S. FDA, 2017).

### C. Expanded access

1. Expanded access (compassionate use) is a pathway to allow patients access to a drug, biologic, or device that has not yet been approved or cleared by the FDA for use outside of a clinical trial.
2. Expanded access may be used when a patient has an immediately life-threatening or severe disease or condition, a patient has exhausted all approved treatment options and is not eligible for a clinical trial, the drug or biologic has demonstrated benefit that outweighs the risk, and there is no compromise to the sponsor's development of the product (Fountzilas et al., 2018; U.S. FDA, 2018c, 2021).
3. Expanded access is not the same as off-label use when an FDA-approved drug or biologic is used for a condition other than what was approved (Fountzilas et al., 2018).
  - a) The most common type of expanded access use is for an individual patient.
    - (1) In this situation, the patient's physician is responsible for submitting paperwork to the FDA, seeking the drug or biologic from the manufacturer, and obtaining IRB approval.
    - (2) This is also referred to as an individual patient expanded access IND or single-patient IND (Fountzilas et al., 2018; U.S. FDA, 2018c, 2021).
  - b) Other expanded access INDs exist based on the size of the planned treatment population. These include intermediate size (i.e., less than 1,000 individuals) and widespread use. Typically, the sponsor undertakes these INDs (Fountzilas et al., 2018; U.S. FDA, 2018c, 2021).
  - c) All of these expanded access IND mechanisms have paperwork requirements from the FDA and require IRB approval. The FDA will assign an IND number, review the application, and notify the physician or sponsor of its decision typically within 30 days (Fountzilas et al., 2018; U.S. FDA, 2018c, 2021).
  - d) Emergency use INDs are an exception in that they can be initiated by phone and reported to the IRB within five working days.
    - (1) The expanded access pathway is often used in oncology (Fountzilas et al., 2018; U.S. FDA, 2018c, 2021).
    - (2) Between 2005 and 2014, more than 10,700 single-patient INDs were submitted to the FDA, with approximately 25% being cancer diagnoses (Fountzilas et al., 2018).

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## SECTION III

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# Cancer Therapeutics

Chapter 6. Chemotherapy

Chapter 7. Hormone Therapy

Chapter 8. Targeted Therapy

Chapter 9. Principles of the Immune System

Chapter 10. Immunotherapy



# CHAPTER 6

## Chemotherapy

### A. Chemotherapy in the treatment of cancer

1. Chemotherapy drugs are chemical agents used to treat cancer. This practice dates back to the 1940s when nitrogen mustard, an alkylating agent, was first noted to have activity against lymphoma, a cancer of the lymph nodes. It is essential to review the principles of chemotherapy to understand how chemotherapy works, including the kinetics of cellular growth. For a general overview of cancer treatment strategies, tumor response definitions, drug resistance, and dosing strategies, see Chapter 4.
2. Cellular kinetics: Three types of cells exist simultaneously.
  - a) Nondividing and terminally differentiated
  - b) Continually proliferating
  - c) Resting cells that can be recruited into the cell cycle at any time (e.g., stem cells)
3. Tumor kinetics (Vlcek, 2022)
  - a) The rate of growth of a tumor is dependent on the following:
    - (1) Growth fraction—the proportion of actively dividing cells
    - (2) Cell cycle time—the average time for a cell in the tumor to go through the entire cell cycle
    - (3) Doubling time—the time it takes for the tumor to double in size. This time is correlated with the length of the cell cycle.
    - (4) Rate of cell loss or death
  - b) Tumor doubling time varies with tumor size.
    - (1) Larger tumors tend to grow slower because of limited blood and oxygen supply.
    - (2) Smaller tumors tend to be more responsive to cytotoxic therapy.
  - c) The cell life cycle is a five-stage reproductive process occurring in healthy and malignant cells (see Figure 6-1).
    - (1) The most important regulatory components of the cell cycle are cyclins and cyclin-dependent kinase (CDK) enzymes.

Cyclins, a family of proteins, activate CDK enzymes and form a complex that promotes cell cycle progression. CDK inhibitors prevent cells from progressing through the cell cycle (Hydbring et al., 2016; Vlcek, 2022).

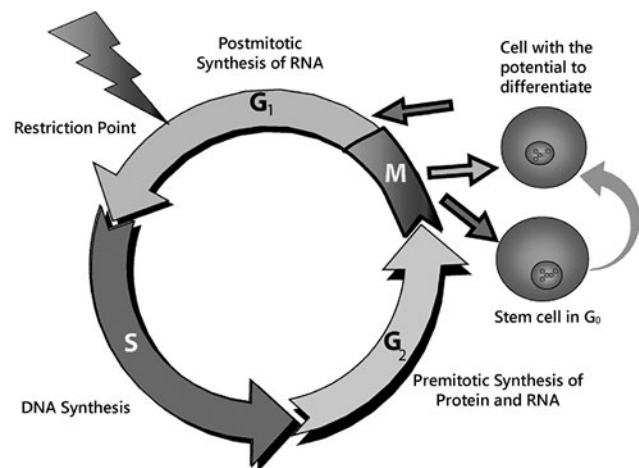
- (2) Chemotherapy agents target different cell cycle phases and halt cell growth and division, leading to cell death. Chemotherapy is administered using various schedules and doses designed to achieve therapeutic goals and based on the principles of cellular kinetics.

### 4. Phases of the cell cycle

#### a) Gap 0 ( $G_0$ )

- (1)  $G_0$  is the resting or dormant phase of the cycle.
- (2) Cells are temporarily out of the cycle and not actively proliferating; however, all other cellular activities occur.

**FIGURE 6-1.** The Cell Cycle



Note. Image courtesy of University of Texas MD Anderson Cancer Center. Used with permission.



- (3) Cells continue in  $G_0$  until a stimulus causes them to reenter the cell cycle.
    - (4) Because they are not actively proliferating, cells in this phase have some protection from exposure to cell cycle-specific chemotherapy agents.
  - b) Gap 1 ( $G_1$ )
    - (1) This is known as the postmitotic phase of the cell cycle.
    - (2) Cells begin the first phase of reproduction and growth by synthesizing the proteins and RNA necessary for cell division.
  - c) Synthesis (S): DNA is replicated.
  - d) Gap 2 ( $G_2$ )
    - (1) The  $G_2$  phase is also known as the premittotic (or postsynthetic) phase.
    - (2) The second phase of protein and RNA synthesis occurs.
    - (3) Preparation for mitotic spindle formation occurs.
    - (4) The cell is now prepared for division.
  - e) Mitosis (M)
    - (1) Cell division occurs.
    - (2) This is the shortest phase of the cell life cycle.
    - (3) Mitosis results in the formation of two daughter cells with exact copies of the parent cell's DNA. Cells either reenter the cell cycle to reproduce or perform the specific functions of the tissue for which they are programmed.
5. Cyclin-CDK complexes (Hydbring et al., 2016; Murphy & Dickler, 2015)
- a) Cyclins are cell cycle kinase regulators (e.g., cyclin D).
  - b) CDKs are cell cycle kinase inhibitors (e.g., CDK4).
  - c) Cyclins and CDKs unite and create complexes that propel the cell through each phase of the cell cycle (e.g., cyclin D-CDK4, cyclin D-CDK6, cyclin E-CDK2 drive  $G_1$ ).
  - d) CDK variations have been linked to tumor formation. For example, CDK6 is overexpressed in many hematologic malignancies, glioblastoma, and lung cancer.
  - e) Anti-CDK/cyclin inhibitors are currently being used to treat patients with metastatic breast cancer. Additional agents are being developed and tested in clinical trials in various cancer types.
- B. Classification of chemotherapy agents
1. Drugs are classified according to their pharmacologic action or effect on cell reproduction (see Table 6-1).
  2. Cell cycle-specific drugs exert effect within a specific phase of the cell cycle (Tortorice, 2018).
    - a) These drugs are most effective when given in divided but frequent doses or continuous infusions. This allows the maximum number of cells to be exposed to the drug at the specific time in their life cycle when they are vulnerable to the drug.
    - b) Classifications include antimetabolites, plant alkaloids (e.g., camptothecins, epipodophyllotoxins, taxanes, vinca alkaloids), and other miscellaneous agents.
  3. Cell cycle-nonspecific drugs exert effect in all phases of the cell cycle, including the  $G_0$  (resting) phase (Tortorice, 2018).
    - a) Cell cycle-nonspecific drugs may effectively treat tumors with more slowly dividing cells.
    - b) If the cancer is sensitive to the agent used, the drug is incorporated into the cell. The cell kill may not be instantaneous but may occur when the cell attempts to divide but encounters irreparable damage.
      - (1) Destruction of tumor cells is directly proportional to the amount of drug administered.
      - (2) These drugs are given intermittently, allowing the individual to recover from dose-limiting toxicities before the drug is repeated at the next interval.
      - (3) The most frequent dose-limiting toxicity is bone marrow suppression.
      - (4) In general, the greater the dose of the drug, the greater the cell kill.
    - c) Classifications include alkylating agents, antitumor antibiotics, hormone therapies, and nitrosoureas.
- C. Chemotherapy classifications (Sparreboom & Baker, 2015)
1. Alkylating agents
    - a) Alkylating agents were the first anticancer agents developed.
    - b) They are cell cycle nonspecific.
    - c) Alkylating agents cause breakage in the DNA helix strand, interfering with DNA replication and ultimately resulting in cell death.
    - d) Dose-limiting toxicities include bone marrow suppression, gastrointestinal toxicities, and organ-specific toxicities (e.g., renal and hepatic, dependent on drug and dose; see Figure 6-2).
    - e) Other effects include carcinogenic and mutagenic effects and impaired fertility.
    - f) Examples include bendamustine, busulfan, cyclophosphamide, cisplatin, and carboplatin.

**TABLE 6-1.** Chemotherapy Agents

| Classification    | Mechanism of Action                                               | Drug                                                             | Route  | Indications                                                                                      | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                                 | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|-------------------|-------------------------------------------------------------------|------------------------------------------------------------------|--------|--------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Alkylating agents | Breaks DNA helix strand, thereby interfering with DNA replication | Bendamustine (Bendeke <sup>®</sup> )                             | IV     | CLL/small lymphocytic leukemia<br>NHL<br>HL<br>Multiple myeloma<br>Waldenström macroglobulinemia | Dose-limiting toxicity: myelosuppression<br>Pyrexia, nausea, vomiting, skin reactions, TLS, hepatotoxicity, irritation to the vein                                                                                                                                                                                                                                                                                           | Infuse over 10 minutes.<br>Bendamustine may inflame and irritate peripheral veins and cause skin and tissue damage (irritant and vesicant properties). Cold compresses should be used for extravasation.<br>Infusion reactions such as chills, pruritus, fever, and rash can be common. Administering corticosteroids, antihistamines, or antipyretics may be helpful.<br>An anaphylactic reaction is rare, especially in second or subsequent cycles.<br>Dose reduction or discontinuation may be necessary for hematologic toxicities. (Teva Pharmaceuticals, 2020) |
|                   |                                                                   | Busulfan (IV: Busulfex <sup>®</sup> ; PO: Myleran <sup>®</sup> ) | IV, PO | HSCT conditioning regimen                                                                        | Dose-limiting toxicities: myelosuppression, pulmonary fibrosis<br>Profound tachycardia, hypertension, chest pain, hyperpigmentation, alopecia, sperm or ovarian suppression, confusion, seizures, mucositis, nausea, vomiting, insomnia, hyperglycemia, blurred vision, second malignancy<br>Increased risk of hepatic sinusoidal obstruction syndrome (previously known as veno-occlusive disease) at AUC > 1,500 mcg × min | Monitor blood counts closely. Administer seizure prophylaxis (phenytoin, levetiracetam, benzodiazepines, or valproic acid).<br>IV form should be administered through a central line. Busulfan is an irritant associated with inflammation and pain during infusion.<br>Busulfan is not compatible with polycarbonate.<br>In oral form, multiple tablets may be placed into a gelatin capsule to facilitate the administration of high oral doses. (DSM Pharmaceuticals; 2018; Otsuka America Pharmaceutical, 2017)                                                   |
|                   |                                                                   | Carboplatin                                                      | IV     | Ovarian cancer<br>Off-label uses in various solid tumors and hematologic malignancies            | Dose-limiting toxicity: thrombocytopenia<br>Neutropenia (myelosuppression more pronounced with renal impairment), nausea, vomiting, hypersensitivity reaction, mild alopecia, skin rash                                                                                                                                                                                                                                      | Carboplatin is an irritant.<br>It exhibits less renal toxicity than cisplatin. Monitor blood counts closely and reduce the dose per protocol. The drug is most toxic to platelet precursors. Monitor for signs of bleeding.<br>Check SCr before each dose (for AUC dosing).                                                                                                                                                                                                                                                                                           |

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**TABLE 6-1.** Chemotherapy Agents (*Continued*)

| Classification                     | Mechanism of Action | Drug                         | Route | Indications                                                                                                                  | Side Effects                                                                                                                                                                                                                                                                                 | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|------------------------------------|---------------------|------------------------------|-------|------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Alkylating agents ( <i>Cont.</i> ) |                     | Carboplatin ( <i>Cont.</i> ) |       |                                                                                                                              |                                                                                                                                                                                                                                                                                              | The emetic potential is based on AUC. High emetic potential is AUC $\geq 4$ ; moderate emetic potential is AUC $< 4$ .<br>Emergency medications should be made available for hypersensitivity reaction, which may occur during any therapy dose or be delayed (around dose 6–8). Most patients can be successfully desensitized via a multistep titration.<br>(National Comprehensive Cancer Network, 2022; Teva Parenteral Medicines, 2016)                                                                                                                                                                                                                                                                                                                                                                                                                 |
|                                    |                     | Chlorambucil (Leukeran®)     | PO    | Chronic lymphocytic leukemia<br>HL<br>NHL                                                                                    | Dose-limiting toxicities: myelosuppression, skin reactions<br>Ovarian or sperm suppression, second malignancy                                                                                                                                                                                | Drugs should be taken on an empty stomach.<br>Chlorambucil should be used with caution in patients with a seizure history and within 1 month of radiation or cytotoxic therapy.<br>(Aspen Global, 2016)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|                                    |                     | Cisplatin                    | IV    | Ovarian cancer<br>Testicular cancer<br>Bladder cancer<br>Off-label uses in various solid tumors and hematologic malignancies | Dose-limiting toxicities: severe nephrotoxicity, myelosuppression<br>Severe acute and delayed nausea, vomiting, ototoxicity (tinnitus and high-frequency hearing loss are most common), hypersensitivity reaction, hypomagnesemia and other electrolyte abnormalities, peripheral neuropathy | Cisplatin is a vesicant at high concentration and an irritant at low concentration. The IV infusion concentration should be $< 0.5$ mg/ml.<br>Adequate hydration should be ensured before, during, and following cisplatin administration. Cisplatin can result in potassium and magnesium depletion and should be monitored and repleted as needed. SCr must be monitored prior to each dose. Renal function must return to normal before subsequent doses are administered; renal toxicity becomes more prolonged and severe with repeated courses.<br>Cisplatin can cause severe nausea and vomiting, necessitating highly effective antiemetics. Nausea and vomiting are dose related and can last up to 5 days. A baseline audiogram should be considered. Ototoxicity is related to the cumulative dose received.<br>(Teva Parenteral Medicines, 2015) |

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**TABLE 6-1.** Chemotherapy Agents (*Continued*)

| Classification                     | Mechanism of Action | Drug               | Route  | Indications                                                                                                                                                    | Side Effects                                                                                                                                                                                                                                                                                                            | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|------------------------------------|---------------------|--------------------|--------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Alkylating agents ( <i>Cont.</i> ) |                     | Cyclophosphamide   | IV, PO | Breast cancer<br>Ovarian cancer<br>Multiple myeloma<br>Leukemias<br>Lymphomas<br>Neuroblastoma<br>Retinoblastoma<br>Mycosis fungoides<br>Off-label use in HSCT | Dose-limiting toxicities:<br>hemorrhagic cystitis, myelosuppression<br>Vomiting, nausea, alopecia; may cause a temporary maxillary burning if administered too quickly, second malignancy, testicular or ovarian failure<br>High dose: acute cardiomyopathy<br>Syndrome of inappropriate antidiuretic hormone secretion | Aggressive hydration and frequent bladder emptying can help reduce the frequency and severity of bladder toxicity and hemorrhagic cystitis. When higher doses are used, mesna may be considered in conjunction with hydration to prevent hemorrhagic cystitis.<br>Previous or concurrent radiation may increase toxicities.<br>Withhold dose for ANC $\leq 1,500/\text{mm}^3$ and platelets $< 50,000/\text{mm}^3$ .<br>PO cyclophosphamide $\geq 100 \text{ mg/m}^2$ daily has a moderate to high emetic potential. Patients must have appropriate antiemetics.<br>(Baxter Healthcare, 2017; West-Ward Pharmaceuticals, 2016) |
|                                    |                     | Dacarbazine        | IV     | HL<br>Metastatic malignant melanoma<br>Off-label use in advanced soft tissue sarcoma                                                                           | Dose-limiting toxicities:<br>severe neutropenia and thrombocytopenia (with a nadir at 2–3 weeks or later)<br>Severe nausea and vomiting for up to 12 hours, anorexia, alopecia, rash, flu-like syndrome (fever, malaise, myalgias), hypotension, hypersensitivity reaction (uncommon), photosensitivity                 | Dacarbazine is an irritant.<br>Protect solution from light.<br>Flu-like syndrome may occur up to 7 days after drug administration; symptoms should be treated.<br>The drug is associated with high emetic potential; patients must have appropriate antiemetics.<br>(Teva Parenteral Medicines, 2020)                                                                                                                                                                                                                                                                                                                          |
|                                    |                     | Ifosfamide (Ifex®) | IV     | Testicular cancer<br>Off-label uses in Ewing sarcoma, advanced soft tissue sarcoma, and relapse refractory lymphomas                                           | Dose-limiting toxicities:<br>hemorrhagic cystitis, myelosuppression<br>Nausea, alopecia, vomiting, neurotoxicity (somnolence, confusion, hallucinations, depressive psychoses, encephalopathy), urotoxicity, cardiotoxicity, pulmonary toxicity,                                                                        | The drug is administered over at least 30 minutes.<br>Patients should receive extensive hydration of at least 2 L IV or oral fluid per day.<br>Hemorrhagic cystitis can be severe and reduced by the prophylactic use of mesna. Mesna can be given in multiple doses (one dose, prior and additional doses after each ifosfamide). It can also be placed in the same bag and administered as a continuous infusion in patients with ifosfamide in specific regimens.                                                                                                                                                           |

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**TABLE 6-1.** Chemotherapy Agents (*Continued*)

| Classification                     | Mechanism of Action | Drug                                                      | Route                      | Indications                                                                                                          | Side Effects                                                                                                                                                                                                                 | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|------------------------------------|---------------------|-----------------------------------------------------------|----------------------------|----------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Alkylating agents ( <i>Cont.</i> ) |                     | Ifosfamide (Ifex®) ( <i>Cont.</i> )                       |                            |                                                                                                                      | Ifosfamide-induced encephalopathy; reports have shown that encephalopathy may spontaneously resolve.                                                                                                                         | Methylene blue and thiamine have been used to treat and prevent ifosfamide-induced encephalopathy. (Baxter Healthcare, 2018; Buesa et al., 2003; Patel, 2006; Pelgrims et al., 2000)                                                                                                                                                                                                                                                                                                                                                                              |
|                                    |                     | Lurbinectedin (Zepzelca®)                                 | IV                         | Small cell lung cancer                                                                                               | Dose-limiting toxicities: myelosuppression, hepatotoxicity<br>Nausea, vomiting, diarrhea                                                                                                                                     | The drug is administered over 60 minutes immediately after reconstitution. It is associated with a moderate emetic potential; patients must have appropriate antiemetics.<br>Consider a central venous catheter to reduce the risk of extravasation resulting in tissue necrosis. (Jazz Pharmaceuticals, 2022)                                                                                                                                                                                                                                                    |
|                                    |                     | Mechlorethamine (Nitrogen mustard, Mustargen®, Valchlor®) | IV, topical, intracavitary | Bronchogenic carcinoma<br>Chronic lymphocytic leukemia<br>CML<br>HL<br>NHL<br>Mycosis fungoides<br>Polycythemia vera | Severe nausea, vomiting, alopecia, myelosuppression, hyperuricemia, pain, phlebitis at IV site, chills, fever, testicular or ovarian failure<br>Topical: dermatitis, pruritus, skin infection, ulceration, hyperpigmentation | Mechlorethamine is a vesicant and an irritant.<br>It is administered through the side arm of a free-flowing IV and flushed with 125–150 ml NS following infusion to minimize phlebitis.<br>If extravasation occurs, the antidote is sodium thiosulfate.<br>Mechlorethamine should be used as soon as possible after preparation (15–30 minutes); it is extremely unstable. (Actelion Pharmaceuticals US, 2016)                                                                                                                                                    |
|                                    |                     | Melphalan (Alkeran®, Evomela®)                            | IV, PO                     | Multiple myeloma<br>Ovarian cancer                                                                                   | Dose-limiting toxicity: myelosuppression<br>Nausea, vomiting, mucositis, hypersensitivity reactions                                                                                                                          | Patients should take the drug on an empty stomach. The application of ice chips to the oral cavity is recommended during high-dose melphalan administration to prevent oral mucositis.<br>Melphalan has been described as an irritant and a vesicant.<br>Two formulations (Alkeran, Evomela):<br>• Alkeran is administered over 15–20 minutes into a fast-running IV solution into an injection port on the IV tubing; it must not be administered by direct injection into a peripheral vein.<br>• Alkeran must be administered within 1 hour of reconstitution. |

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**TABLE 6-1.** Chemotherapy Agents (*Continued*)

| Classification                     | Mechanism of Action | Drug                                                  | Route | Indications                                                                              | Side Effects | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|------------------------------------|---------------------|-------------------------------------------------------|-------|------------------------------------------------------------------------------------------|--------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Alkylating agents ( <i>Cont.</i> ) |                     | Melphalan<br>(Alkeran®, Evomela®)<br>( <i>Cont.</i> ) | IV    | Colorectal cancer<br>Off-label uses in various solid tumors and hematologic malignancies |              | <ul style="list-style-type: none"> <li>Evomela is administered over 30 minutes via central access.</li> <li>Evomela is stable for 4 hours at room temperature.</li> </ul> <p>Dose should be reduced in renal insufficiency (blood urea nitrogen <math>\geq</math> 30 mg/dl). The drug is administered through a central access.<br/>(GlaxoSmithKline, 2012; Lilleby et al., 2006; Spectrum Pharmaceuticals, 2019)</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|                                    |                     | Oxaliplatin<br>(Eloxatin®)                            |       |                                                                                          |              | <p>Oxaliplatin is not compatible with sodium chloride or other chloride-containing solutions. Flush with D<sub>5</sub>W following infusion.</p> <p>Persistent (&gt; 14 days) peripheral sensory neuropathy characterized by paresthesias, dysesthesias, and hyperesthesias may occur that can interfere with daily activities (writing, buttoning, walking). Oxaliplatin has been described as an irritant and a vesicant.</p> <p>Monitor for acute, reversible effects and persistent neurotoxicity.</p> <p>For 3–4 days after therapy, patients should avoid consuming cold drinks and foods and breathing cold air (cover mouth with scarf).</p> <p>Dose reduce in patients with severe renal impairment (CrCl &lt; 30 ml/min).</p> <p>Serious hypersensitivity reactions may occur. Reactions occur at a median of 7–9 doses.</p> <p>Rechallenge by prolonging the infusion time and premedicate with antihistamines and a corticosteroid for mild reactions. A multistep desensitization protocol could help with tolerance in patients with prior reactions.<br/>(Sanofi-Aventis U.S., 2020)</p> |

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**TABLE 6-1.** Chemotherapy Agents (Continued)

| Classification            | Mechanism of Action | Drug                    | Route  | Indications                                                                                                         | Side Effects                                                                                                                                                                                                     | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|---------------------------|---------------------|-------------------------|--------|---------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Alkylating agents (Cont.) |                     | Temozolomide (Temodar®) | IV, PO | Refractory anaplastic astrocytoma<br>Newly diagnosed glioblastoma multiforme<br>Off-label use in malignant melanoma | Dose-limiting toxicity: myelosuppression<br>Nausea, vomiting, headache, fatigue, hepatotoxicity, constipation, rash, alopecia                                                                                    | IV: The drug is administered over 90 minutes. Temozolomide is only compatible with 0.9% sodium chloride.<br>PO: Do not open capsules.<br>Consider bedtime administration for oral dosing to decrease nausea and vomiting.<br>Oral temozolomide has moderate to high emetic potential; patients must have a scheduled antiemetic with each dose.<br>Do not administer temozolomide if patients have had an allergic reaction to dacarbazine.<br>Administer <i>Pneumocystis jirovecii</i> pneumonia prophylaxis with trimethoprim-sulfamethoxazole in patients receiving temozolomide with concurrent radiation. (Merck, 2019) |
|                           |                     | Thiotepa (Tepa-dina®)   | IT, IV | Off-label use in HSCT                                                                                               | Dose-limiting toxicity: myelosuppression<br>Fatigue, weakness, fever, hypersensitivity reaction, ovarian or sperm suppression, nausea, vomiting, pain at the infusion site, rash, alopecia, skin burn, mucositis | Use with caution in patients with severe renal or hepatic dysfunction.<br>Thiotepa used in the transplant setting can cause severe skin irritation. Frequent showering immediately following and during the first 48 hours after administration helps remove the chemical from the skin. Additionally, avoid tapes and skin adherents during treatment and for 48 hours following administration.<br>Filter through a 0.22-micron filter prior to administration. (West-Ward Pharmaceuticals, 2019)                                                                                                                          |

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**TABLE 6-1.** Chemotherapy Agents (*Continued*)

| Classification                     | Mechanism of Action                                                                                                                                                                                      | Drug                           | Route      | Indications                     | Side Effects                                                                                                                                                                                                                                           | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|------------|---------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Alkylating agents ( <i>Cont.</i> ) |                                                                                                                                                                                                          | Trabectedin (Yondelis®)        | IV         | Leiomyosarcoma<br>Liposarcoma   | Dose-limiting toxicities: myelosuppression (neutropenic sepsis), hepatotoxicity, cardiomyopathy<br>Rhabdomyolysis, capillary leak syndrome, nausea, fatigue, vomiting, constipation, decreased appetite, diarrhea, peripheral edema, dyspnea, headache | Primary prophylaxis with granulocyte-colony-stimulating factor is required. Moderate to high emetic potential exists. Patients must have appropriate antiemetics prior to each dose.<br>Trabectedin is administered as a 24-hour continuous infusion and must be given through a central line. A 0.2-micron filter must be used.<br>Trabectedin is a vesicant; extravasation can result in severe tissue injury.<br>Premedicate with 20 mg IV dexamethasone 30 minutes prior to infusion.<br>Dose reduce in patients with hepatic impairment.<br>Monitor creatine phosphokinase prior to each dose due to the risk of rhabdomyolysis. (Janssen Biotech, 2020)                                                                                                                                                                                                                                                                                       |
| Antimetabolites                    | Pyrimidine nucleoside analog of cytidine that inhibits DNA/RNA methyltransferases; reduces DNA and RNA methylation, alters DNA gene expression, decreases RNA stability, and decreases protein synthesis | Azacitidine (Onureg®, Vidaza®) | IV, SC, PO | AML<br>Myelodysplastic syndrome | Dose-limiting toxicities: myelosuppression, elevated SCr, nausea, vomiting, diarrhea, fatigue, fever, erythema at the injection site, constipation                                                                                                     | IV: Mix in 50–100 ml NS or lactated Ringer's solution only. Infuse over 10–40 minutes. The administration should be completed within 1 hour of reconstitution.<br>Ensure patients take a prophylactic antiemetic prior to each dose for the first 2 cycles of PO azacitidine.<br>SC: Resuspend suspension immediately before administration by rolling syringe between palms; the solution should be uniformly cloudy. It is stable at room temperature for 1 hour and under refrigeration for 8 hours (when reconstituted using room-temperature water).<br>Divide doses > 3 ml into multiple syringes and inject into separate sites. Administer new injections at least 1 inch from the old site.<br>To minimize skin irritation, ensure that the needle is empty of the drug and do not expel air into the needle before giving the injection. Do not use ice on the injection site, as it may decrease drug absorption. (Celgene, 2016, 2020b) |

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**TABLE 6-1.** Chemotherapy Agents (*Continued*)

| Classification                      | Mechanism of Action                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Drug                      | Route | Indications                                                                                                                                                       | Side Effects                                                                                                                                                                                                | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|-------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Antimetabolites<br>( <i>Cont.</i> ) | <p>Prodrug of 5-FU; after ingestion, undergoes hydrolysis in the liver to form 5-FU; is a nucleoside metabolic inhibitor that interferes with the synthesis of DNA and, to a lesser extent, inhibits the formation of RNA</p> <p>Most other anti-metabolites interfere with one or more enzymes or their reactions that are necessary for DNA synthesis. They affect DNA synthesis by acting as a substitute to the metabolites that would be used in the normal metabolism (e.g., antifolates interfere with the use of folic acid).</p> | Capecitabine<br>(Xeloda®) | PO    | <p>Colon cancer</p> <p>Metastatic breast cancer</p> <p>Metastatic colorectal cancer</p> <p>Off-label use in pancreatic cancers and hepatobiliary tract cancer</p> | <p>Dose-limiting toxicities:</p> <p>Diarrhea, palmar-plantar erythrodysesthesia (hand-foot syndrome)</p> <p>Mucositis, nausea, vomiting, myelosuppression, increased bilirubin, fatigue, cardiotoxicity</p> | <p>Capecitabine can significantly affect prothrombin time/international normalized ratio and increase bleeding risk. Recommend switching patients to alternative anticoagulants such as direct-acting oral anticoagulants or enoxaparin. Monitor prothrombin time/international normalized ratio closely for those on concomitant warfarin and capecitabine.</p> <p>Administer with food and water. Taking the drug on an empty stomach will increase absorption, increasing toxicities.</p> <p>Dose reduction is necessary for older adult patients and those with CrCl &lt; 50 ml/min.</p> <p>Ensure patients have antidiarrheal medication when starting capecitabine.</p> <p>Concomitant use of capecitabine and proton pump inhibitor (e.g., pantoprazole, omeprazole) may reduce efficacy and survival and should be avoided if necessary.</p> <p>Uridine triacetate (Vistogard®) is U.S. Food and Drug Administration approved for the emergency treatment of 5-FU or capecitabine overdose regardless of the presence of symptoms or in patients who exhibit early-onset (within 96 hours of administration) severe or life-threatening cardiac or CNS toxicity and/or early-onset (within 96 hours of administration) unusually severe adverse reactions (GI toxicities and/or neutropenia). Uridine triacetate is a prodrug of uridine, which competes with 5-fluorouridine triphosphate, a toxic metabolite of 5-FU, for incorporation into RNA during RNA sequencing. (Genentech, 2021; Wellstat Therapeutics, 2017)</p> |

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**TABLE 6-1.** Chemotherapy Agents (*Continued*)

| Classification                      | Mechanism of Action | Drug                     | Route      | Indications                                                        | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|-------------------------------------|---------------------|--------------------------|------------|--------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Antimetabolites<br>( <i>Cont.</i> ) |                     | Cladribine               | IV         | Hairy cell leukemia<br>Off-label use for induction therapy for AML | Dose-limiting toxicities: myelosuppression, neurotoxicity<br>Fever, nausea, vomiting, hypersensitivity reaction, TLS, nephrotoxicity (high-dose therapy)                                                                                                                                                                                                                                                                                                                              | The drug can be given as a bolus infusion over 2–4 hours (more popular) or as a continuous infusion.<br>Use with caution in patients with liver and renal dysfunction.<br>(Fresenius Kabi USA, 2016b)                                                                                                                                                                                                                                                                                                                                                             |
|                                     |                     | Clofarabine<br>(Clolar®) | IV         | Relapsed or refractory ALL in patients aged 1–21 years             | Dose-limiting toxicities: bone marrow suppression (including anemia, leukopenia, thrombocytopenia, neutropenia, and febrile neutropenia), infection, hepatobiliary toxicity, renal toxicity<br>Nausea; vomiting; diarrhea; rare cases of systemic inflammatory response syndrome/capillary leak syndrome and cardiotoxicity, including tachycardia, pericardial effusion, and left ventricular systolic dysfunction; TLS; headache; pruritus; rash; palmar-plantar erythrodysesthesia | Administer IV over 2 hours daily for 5 consecutive days of a 28-day cycle.<br>Use prophylactic steroids to prevent systemic inflammatory response syndrome and capillary leak syndrome.<br>Give allopurinol if hyperuricemia is expected.<br>Monitor respiratory status and blood pressure during infusion.<br>Monitor renal and liver function during the days of administration.<br>Dose reduction is necessary in patients with renal impairment (CrCl < 60 ml/min).<br>Monitor hematologic status closely following treatment.<br>(Sanofi-Aventis U.S., 2016) |
|                                     |                     | Cytarabine               | IT, IV, SC | ALL<br>AML<br>CML<br>CNS leukemia                                  | Dose-limiting toxicity: myelosuppression<br>Nausea, vomiting, anorexia, fever, mucositis, diarrhea, hepatic dysfunction, rash, pruritus, localized pain and thrombophlebitis at the IV site<br>High-dose (1–3 g/m <sup>2</sup> ): cerebellar toxicity, keratitis (treated with ophthalmic steroid drops), dermatologic toxicities                                                                                                                                                     | Determine if the ordered dose is standard or high; administer according to institutional guidelines.<br>Toxicities vary depending on the rate and dose of cytarabine ordered.<br>Continuous-infusion cytarabine is associated with pulmonary toxicity (fluid overload), and bolus administration is associated with cerebellar toxicities. Specific nursing interventions are warranted for each.<br>See Chapters 17 and 24 for information on pulmonary toxicities and neurotoxicity.                                                                            |

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**TABLE 6-1.** Chemotherapy Agents (*Continued*)

| Classification                      | Mechanism of Action                                                                                                                                                                                                  | Drug                                  | Route          | Indications                                | Side Effects                                                                                                                                                                                                                                                  | Nursing Considerations                                                                                                                                                                                                                                                                 |
|-------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|----------------|--------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Antimetabolites<br>( <i>Cont.</i> ) |                                                                                                                                                                                                                      | Cytarabine<br>( <i>Cont.</i> )        |                |                                            |                                                                                                                                                                                                                                                               | Ensure patients have ophthalmic drops when high-dose cytarabine is given ( $\geq 1 \text{ g/m}^2$ ); ophthalmic drops are to start prior to cytarabine and continue for 48 hours after the last cytarabine dose. (Hospira, 2020a)                                                      |
|                                     | Believed to cause hypomethylation of DNA and direct cytotoxicity on abnormal hematopoietic cells in the bone marrow; abnormal cells, including cancer cells, no longer respond to healthy growth control mechanisms. | Decitabine IV: (Dacogen®)             | IV             | Myelodysplastic syndrome                   | Myelosuppression, fever, fatigue, nausea, diarrhea                                                                                                                                                                                                            | For IV administration, use preservative-free NS. (Eisai, 2018)                                                                                                                                                                                                                         |
|                                     | See decitabine; cedazuridine increases exposure by inhibiting cytidine deaminase, which degrades decitabine.                                                                                                         | Decitabine and cedazuridine (Inqovi®) | PO             | Myelodysplastic syndrome                   | Myelosuppression, fatigue, constipation, hemorrhage, myalgia, mucositis, arthralgia, nausea, diarrhea, rash, dizziness, febrile neutropenia, edema, headache, cough, decreased appetite, upper respiratory tract infection, pneumonia, increased transaminase | Instruct patients to take on an empty stomach at the same time each day. Tablets should be swallowed whole. They should not be cut, crushed, or chewed. Obtain CBC prior to initiation, prior to each cycle and as needed for monitoring response and toxicity. (Taiho Oncology, 2020) |
|                                     |                                                                                                                                                                                                                      | Floxuridine (FUDR)                    | Intra-arterial | GI adenocarcinoma with metastasis to liver | Myelosuppression, nausea, vomiting, diarrhea, stomatitis, mucositis, localized erythema, alopecia, photosensitivity, darkening of the veins, abdominal pain, gastritis, enteritis, hepatotoxicity                                                             | Nurse and provider training and competency should be verified before accessing and instilling floxuridine or a lock solution (e.g., heparin) in a hepatic arterial pump. Assess patient for signs and symptoms of infection at port site. (Fresenius Kabi USA, 2016c)                  |

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**TABLE 6-1.** Chemotherapy Agents (*Continued*)

| Classification                      | Mechanism of Action                                                                                                                                                                   | Drug                                  | Route       | Indications                                                                                                 | Side Effects                                                                                                                                                                                                                                                                    | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|-------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|-------------|-------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Antimetabolites<br>( <i>Cont.</i> ) |                                                                                                                                                                                       | Fludarabine                           | IV          | Chronic lymphocytic leukemia<br>Off-label use in HSCT                                                       | Dose-limiting toxicity: myelosuppression<br>TLS, nausea, vomiting, diarrhea, rash, neurotoxicity, interstitial pneumonitis, weakness, hemolytic anemia, cough, infection                                                                                                        | Administer as a 30-minute infusion.<br>Use with caution in patients with renal impairment.<br>(Teva Parenteral Medicines, 2017b)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                     | Combination of a thymidine-based nucleoside analog and a thymidine phosphorylase inhibitor that incorporates into DNA, interferes with DNA synthesis, and inhibits cell proliferation | Trifluridine and tipiracil (Lonsurf®) | PO          | Previously treated metastatic colorectal cancer                                                             | Anemia, neutropenia, fatigue, nausea, vomiting, diarrhea, abdominal pain, pyrexia, embryo-fetal toxicity                                                                                                                                                                        | Administer 35 mg/m <sup>2</sup> PO twice daily on days 1–5 and days 8–12 of each 28-day cycle.<br>Take within 1 hour after meals 12 hours apart.<br>Round dose to nearest 5 mg increment.<br>Do not administer if ANC < 500/mm <sup>3</sup> or platelets < 50,000/mm <sup>3</sup> .<br>(Taiho Oncology, 2019)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|                                     | Nucleoside metabolic inhibitor that interferes with the synthesis of DNA and, to a lesser extent, inhibits the formation of RNA                                                       | 5-FU (Adrucil®)                       | IV, topical | Basal cell carcinoma (topical)<br>Breast cancer<br>Colorectal cancer<br>Gastric cancer<br>Pancreatic cancer | Dose-limiting toxicities: mucositis, myelosuppression<br>Nausea, anorexia, vomiting, diarrhea, alopecia, ocular toxicities (increased lacrimation, photosensitivity), darkening of the veins, dry skin, cardiotoxicity (rare), neurotoxicity, palmar-plantar erythrodysesthesia | Ensure that patients take year-round photosensitivity precautions; encourage sunscreen use if patients must be exposed.<br>Leucovorin is often given immediately before 5-FU to enhance 5-FU activity.<br>A very different toxicity profile exists between 5-FU IV push versus continuous infusion. 5-FU IV push will result in more mucositis and myelosuppression, whereas continuous infusion will cause more diarrhea and palmar-plantar erythrodysesthesia.<br>Apply ice chips to the oral cavity 10–15 minutes pre- and post-IV bolus dose of 5-FU to reduce oral mucositis in patients with GI malignancies.<br>Uridine triacetate (Vistogard) is U.S. Food and Drug Administration approved for the emergency treatment of 5-FU or capecitabine overdose regardless of the presence of symptoms or in patients who exhibit early-onset (within 96 hours of administration) severe or life-threatening |

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**TABLE 6-1.** Chemotherapy Agents (*Continued*)

| Classification                      | Mechanism of Action | Drug                                   | Route              | Indications                                                                                                                                                                                                              | Side Effects                                                                                                                                                                                                                                                          | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-------------------------------------|---------------------|----------------------------------------|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Antimetabolites<br>( <i>Cont.</i> ) |                     | 5-FU<br>(Adrucil®)<br>( <i>Cont.</i> ) |                    |                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                       | cardiac or CNS toxicity and/or early-onset (within 96 hours of administration) unusually severe adverse reactions (GI toxicities and/or neutropenia). Uridine triacetate is a prodrug of uridine, which competes with 5-fluorouridine triphosphate, a toxic metabolite of 5-FU, for incorporation into RNA during RNA sequencing.<br>(Teva Parenteral Medicines, 2017a; Wellstat Therapeutics, 2017)                                                                                                    |
|                                     |                     | Gemcitabine<br>(Gemzar®)               | IV, intra-vesical  | Breast cancer<br>Pancreatic cancer<br>NSCLC<br>Ovarian cancer<br>Off-label indications for various solid tumor and hematologic malignancies, including soft tissue sarcoma and relapsed/refractory lymphomas             | Dose-limiting toxicity: myelosuppression (especially thrombocytopenia)<br>Nausea; vomiting; flu-like symptoms, including fever, headache, arthralgias, and myalgias; rash; peripheral edema; dyspnea; pulmonary toxicity with increased infusion time; hepatotoxicity | Gemcitabine is an irritant. Infuse over 30 minutes for the majority of indications. When used in soft tissue sarcoma, it is often given at a fixed rate of 10 mg/m <sup>2</sup> /min; more prolonged infusion will result in more hematologic toxicity. Increased (severe and life-threatening) toxicity may occur when gemcitabine is administered within 7 days of radiation therapy.<br>(Eli Lilly and Company, 2019b)                                                                               |
|                                     |                     | 6-Mercaptopurine (6-MP; Purinethol®)   | PO                 | ALL                                                                                                                                                                                                                      | Myelosuppression, hepatotoxicity, mucositis, nausea, vomiting, anorexia, hyperuricemia, hyperuricosuria, alopecia, rash, hyperpigmentation                                                                                                                            | Reduce oral dose by 75% when used concurrently with allopurinol. Instruct patients to take on an empty stomach.<br>(Kantarjian et al., 2000; Mylan Pharmaceuticals, 2013)                                                                                                                                                                                                                                                                                                                               |
|                                     |                     | Methotrexate                           | IM, IT, IV, PO, SC | Breast cancer<br>Choriadenoma destruens<br>CNS metastasis<br>Gestational choriocarcinoma<br>Gestational trophoblastic tumor<br>Hydatidiform mole<br>Leukemia<br>NHL<br>Osteosarcoma<br>Psoriasis<br>Rheumatoid arthritis | Dose-limiting toxicities: hepatotoxicity, renal toxicity<br>Mucositis, nausea, vomiting, myelosuppression, oral or GI ulceration, pneumonitis, photosensitivity, neurotoxicity associated with high-dose therapy                                                      | High-dose methotrexate doses are adjusted for patients with renal dysfunction. High doses must be followed by timely administration of leucovorin and alkaline hydration. Follow the dosing schedule carefully. Monitor serum methotrexate levels until ≤ 0.05–0.1 mcmol/L. Monitor urine pH and maintain ≥ 7 before and until serum methotrexate levels ≤ 0.05 mcmol/L. Depending on methotrexate clearance, some patients may require additional leucovorin rescue and serum methotrexate monitoring. |

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**TABLE 6-1.** Chemotherapy Agents (*Continued*)

| Classification                      | Mechanism of Action | Drug                             | Route | Indications                                 | Side Effects                                                                                                                                                                                                  | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|-------------------------------------|---------------------|----------------------------------|-------|---------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Antimetabolites<br>( <i>Cont.</i> ) |                     | Methotrexate<br>( <i>Cont.</i> ) |       |                                             |                                                                                                                                                                                                               | Instruct patients on strict oral care.<br>Ensure that patients avoid taking multivitamins with folic acid.<br>Multiple drug interactions (nonsteroidal anti-inflammatory drugs, alcohol, aspirin, warfarin, and aminoglycosides) are possible.<br>Glucarpidase (Voraxaze®) is U.S. Food and Drug Administration approved for patients with delayed methotrexate clearance due to renal impairment. This drug reduces systemic methotrexate levels by rapidly converting methotrexate to glutamate and 4-deoxy-4-amino-N <sup>10</sup> -methylpteroic acid.<br>(BTG International, 2019; Fresenius Kabi USA, 2020) |
|                                     |                     | Nelarabine<br>(Arranon®)         | IV    | T-cell ALL<br>T-cell lymphoblastic lymphoma | Dose-limiting toxicity: neurotoxicity<br>Myelosuppression, headache, nausea, vomiting, diarrhea, constipation, cough, fatigue, peripheral neuropathy, dyspnea, neurotoxicities (somnolence, seizures, ataxia) | Nelarabine is administered as an undiluted IV infusion over 2 hours for adult patients and 1 hour for pediatric patients.<br>Administer with appropriate supportive care medications to prevent hyperuricemia and TLS.<br>Discontinue for ≥ grade 2 neurologic events (severe somnolence, seizure, and peripheral neuropathy).<br>Use caution in patients with renal or hepatic dysfunction.<br>(Novartis Pharmaceuticals, 2019)                                                                                                                                                                                  |
|                                     |                     | Pemetrexed<br>(Alimta®)          | IV    | Mesothelioma<br>Nonsquamous NSCLC           | Myelosuppression, fatigue, nausea, vomiting, anorexia, chest pain, dyspnea (vitamin supplementation reduces these side effects)<br>Renal and liver toxicity                                                   | Infuse over 10 minutes.<br>To reduce treatment-related hematologic and GI toxicities, administer folic acid 400–1,000 mcg PO daily starting 1 week prior to the first cycle and daily for 3 weeks after the final cycle.<br>Give vitamin B <sub>12</sub> 1,000 mcg IM injection 1 week before the first cycle and repeat every 9 weeks until treatment is completed.<br>Dexamethasone 4 mg given twice daily for 3 days, starting the day before treatment, decreases the incidence of rash.                                                                                                                      |

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**TABLE 6-1.** Chemotherapy Agents (*Continued*)

| Classification                      | Mechanism of Action | Drug                                        | Route | Indications                | Side Effects                                                                                                                                                                                                          | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|-------------------------------------|---------------------|---------------------------------------------|-------|----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Antimetabolites<br>( <i>Cont.</i> ) |                     | Pemetrexed<br>(Alimta®)<br>( <i>Cont.</i> ) |       |                            |                                                                                                                                                                                                                       | Hold treatment if ANC < 1,500/mm <sup>3</sup> , platelets < 100,000/mm <sup>3</sup> , or CrCl < 45 ml/min. Monitor renal and liver function. Patients should avoid using nonsteroidal anti-inflammatory drugs while on pemetrexed, as concurrent use may increase the risk of renal damage. (Eli Lilly and Company, 2019a)                                                                                                                                                                                                                                                                                                                                                                    |
|                                     |                     | Pentostatin<br>(Nipent™)                    | IV    | Hairy cell leukemia        | Dose-limiting toxicity: myelosuppression<br>Acute pulmonary edema, hypotension, fever, chills, nausea, vomiting, rash, renal toxicity, confusion, hepatic enzyme elevation, heightened infection risk, cough, cardiac | Administer with 500–1,000 ml D <sub>5</sub> W in 0.5 NS prior to infusion and an additional 500 ml after infusion. Do not administer with fludarabine, carmustine, etoposide, or high-dose cyclophosphamide. (Hospira, 2019)                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|                                     |                     | Pralatrexate<br>(Foloty®)                   | IV    | Peripheral T-cell lymphoma | Dose-limiting toxicity: myelosuppression<br>Mucositis, dermatologic reactions, hepatotoxicity, edema, fatigue                                                                                                         | Pralatrexate is administered as an IV push over 3–5 minutes. Consider dose reduction in patients with impaired renal function (estimated glomerular filtration rate < 30 ml/min/1.73 m <sup>2</sup> ). Prophylactic folic acid and vitamin B <sub>12</sub> supplements must be given. Supplement patients with vitamin B <sub>12</sub> 1,000 mcg IM every 8–10 weeks and folic acid 1–1.25 mg PO daily. Monitor liver and renal function.<br><br>Consider adding oral leucovorin 25 mg 3 times daily for 6 doses to help reduce oral mucositis. Leucovorin should be initiated 24 hours after each pralatrexate dose. (Acrotech Biopharma, 2020; National Comprehensive Cancer Network, 2022) |
|                                     |                     | Thioguanine<br>(6-TG; Tabloid®)             | PO    | ALL                        | Dose-limiting toxicity: myelosuppression<br>Hyperuricemia, nausea, hepatotoxicity, diarrhea                                                                                                                           | Monitor liver function. Patients should take the drug on an empty stomach to reduce the risk of nausea and vomiting. (Aspen Global, 2012b)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

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**TABLE 6-1.** Chemotherapy Agents (*Continued*)

| Classification        | Mechanism of Action                                      | Drug                                    | Route                     | Indications                                                                                                                          | Side Effects                                                                                                                                                                                                                                                    | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|-----------------------|----------------------------------------------------------|-----------------------------------------|---------------------------|--------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Antitumor antibiotics | Binds with DNA, thereby inhibiting DNA and RNA synthesis | Bleomycin                               | IM, intra-pleural, IV, SC | HL<br>Malignant pleural effusion<br>NHL<br>Testicular cancer<br>Squamous cell cancers of the head and neck, cervix, vulva, and penis | Dose-limiting toxicities: hypersensitivity or anaphylactic reaction (rare), pulmonary toxicity<br>Hyperpigmentation, alopecia, photosensitivity, renal toxicity, hepatotoxicity, fever, chills, erythema, rash, mucositis                                       | Bleomycin is ordered in units. Bleomycin is not compatible with D <sub>5</sub> W. Patients who have received prior bleomycin are at risk for pulmonary toxicity when exposed to oxygen during surgery. Ensure that patients and family members understand the lifelong necessity of disclosing previous use of bleomycin when future needs for anesthesia occur to prevent a fatal episode of pulmonary failure. Because of the dose-related incidence of pulmonary fibrosis, the cumulative lifetime dose should not exceed 400 units. Pulmonary function tests are recommended at initiation of bleomycin and every 1–2 months thereafter. Consider stopping the drug if a 30%–35% decrease from pretreatment values occurs. Acetaminophen and an antihistamine may decrease fever and chills in the first 24 hours after administration. Consider dose reductions in patients with CrCl < 50 ml/min. (Fresenius Kabi USA, 2016a) |
|                       |                                                          | Dactinomycin (Actinomycin-D; Cosmegen®) | IV                        | Pediatric rhabdomyosarcoma<br>Gestational trophoblastic disease<br>Ewing sarcoma<br>Testicular cancer<br>Wilms tumor                 | Dose-limiting toxicity: myelosuppression<br>Nausea, vomiting, alopecia, mucositis, diarrhea, ovarian or sperm suppression, radiation recall (hyperpigmentation of previously irradiated areas), sinusoidal obstruction syndrome, renal toxicity, hepatotoxicity | Dactinomycin is a vesicant; extravasation can result in severe tissue injury. Administer through the side port of a free-flowing IV. Dactinomycin is highly toxic and corrosive to soft tissues; inhalation and contact with the eyes must be avoided. This drug may be ordered in micrograms; check the dose carefully. Dactinomycin is contraindicated in patients with concurrent or recent chicken pox or herpes zoster. Avoid within 2 months of radiation therapy for right-sided Wilms tumor. (Recordati Rare Diseases, 2018)                                                                                                                                                                                                                                                                                                                                                                                                |

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**TABLE 6-1.** Chemotherapy Agents (Continued)

| Classification                        | Mechanism of Action                                      | Drug                                           | Route            | Indications                                           | Side Effects                                                                                                                                 | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|---------------------------------------|----------------------------------------------------------|------------------------------------------------|------------------|-------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Antitumor antibiotics<br>(Cont.)      |                                                          | Mitomycin C (Mutamycin®)                       | Intravesical, IV | Bladder cancer<br>Pancreatic cancer<br>Gastric cancer | Dose-limiting toxicity: myelosuppression<br>Nausea, vomiting, anorexia, fever, renal toxicity, pulmonary toxicity, fatigue                   | The drug is purple-blue in color. Mitomycin is a vesicant; extravasation can result in severe tissue injury. Administer through the side port of a free-flowing IV. Nadir occurs within 8 weeks after treatment begins (average of 4 weeks). Acute shortness of breath and bronchospasm can occur very suddenly when this drug is given with a vinca alkaloid. Withhold doses for platelets < 100,000/mm <sup>3</sup> or white blood cells < 4,000/mm <sup>3</sup> . Do not use in patients with SCr > 1.7 mg/dl. Hemolytic uremic syndrome has been seen with a single dose ≥ 60 mg. Mitomycin is contraindicated in patients with coagulation disorders. The prepared solution needs to be protected from light. (Accord BioPharma, 2016) |
| Antitumor antibiotics: anthracyclines | Binds with DNA, thereby inhibiting DNA and RNA synthesis | Daunorubicin (Cerubidine®)                     | IV               | ALL in children<br>AML                                | Dose-limiting toxicities: myelosuppression, cardiotoxicity<br>Nausea, vomiting, alopecia, hyperuricemia, radiation recall, red-colored urine | The drug is red in color. Daunorubicin is a vesicant; extravasation can result in severe tissue injury. Administer through the side arm of a free-flowing IV. Dose reduce in patients with hepatic or renal impairment. Test cardiac ejection fraction before starting therapy. The maximum lifetime dose is 550 mg/m <sup>2</sup> in adults without cardiovascular risk factors and 400 mg/m <sup>2</sup> in adults receiving chest irradiation. (Teva Parenteral Medicines, 2014)                                                                                                                                                                                                                                                         |
|                                       |                                                          | Daunorubicin and cytarabine liposome (Vyxeos™) | IV               | AML                                                   | Dose-limiting toxicities: myelosuppression, cardiotoxicity, hypersensitivity reaction<br>Hemorrhage events, copper overload                  | Administer over 90 minutes through a central line. Maximum lifetime daunorubicin dose is 550 mg/m <sup>2</sup> in adults without cardiovascular risk factors and 400 mg/m <sup>2</sup> in adults receiving chest irradiation.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

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**TABLE 6-1.** Chemotherapy Agents (*Continued*)

| Classification                                            | Mechanism of Action | Drug                                                               | Route | Indications                                                                                                                                                                    | Side Effects                                                                                                                                                                              | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|-----------------------------------------------------------|---------------------|--------------------------------------------------------------------|-------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Antitumor antibiotics: anthracyclines<br>( <i>Cont.</i> ) |                     | Daunorubicin and cytarabine liposome (Vyxeos™)<br>( <i>Cont.</i> ) | IV    | ALL<br>Bladder cancer<br>Breast cancer<br>Bronchogenic carcinoma<br>HL<br>Neuroblastoma<br>NHL<br>Ovarian cancer<br>Wilms tumor<br>Sarcoma<br>Gastric cancer<br>Thyroid cancer | Dose-limiting toxicities: myelosuppression, cardiotoxicity, hepatotoxicity<br>Nausea, vomiting, alopecia, mucositis, radiation recall, hyperuricemia, photosensitivity, red-colored urine | Vyxeos contains copper gluconate; copper toxicity is possible in patients with Wilson disease.<br>Daunorubicin is a vesicant; extravasation can result in severe tissue injury. (Jazz Pharmaceuticals, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|                                                           |                     | Doxorubicin (Adriamycin®)                                          |       |                                                                                                                                                                                |                                                                                                                                                                                           | The drug is red in color.<br>Doxorubicin is a vesicant; extravasation can result in severe tissue injury.<br>Administer through the side arm of a free-flowing IV or via continuous infusion through a central catheter only.<br>Administer dexrazoxane if extravasation occurs. Apply ice immediately to the extravasation site. See Chapter 13.<br>Dose reduce in patients with elevated serum total bilirubin.<br>Test cardiac ejection fraction before starting therapy.<br>Do not exceed a lifetime cumulative dose of 550 mg/m <sup>2</sup> (450 mg/m <sup>2</sup> if the patients have had prior chest irradiation or concomitant cyclophosphamide treatment).<br>Consider initiating dexrazoxane for cardiac protection in patients who have received a cumulative dose of 300 mg/m <sup>2</sup> and continue doxorubicin treatment.<br>The risk of cardiac toxicity is increased when given as an IV push versus IV infusion or continuous infusion.<br>(Pfizer, 2020a; van Dalen et al., 2016) |

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**TABLE 6-1.** Chemotherapy Agents (*Continued*)

| Classification                                         | Mechanism of Action | Drug                           | Route | Indications                                                       | Side Effects                                                                                                                                                                                                                                               | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|--------------------------------------------------------|---------------------|--------------------------------|-------|-------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Antitumor antibiotics: anthracyclines ( <i>Cont.</i> ) |                     | Doxorubicin liposomal (Doxil®) | IV    | AIDS-related Kaposi sarcoma<br>Multiple myeloma<br>Ovarian cancer | Dose-limiting toxicities: myelosuppression, cardiotoxicity, infusion-related reactions<br>Nausea, vomiting, alopecia, mucositis, arrhythmia, amenorrhea, radiation recall, palmar-plantar erythrodysesthesia, hypersensitivity reaction, red-colored urine | The drug is red in color.<br>Doxorubicin liposomal is an irritant with vesicant properties; take caution to avoid extravasation.<br>The same warnings as with conventional doxorubicin apply regarding cardiovascular complications.<br>The drug is less cardiotoxic compared to regular doxorubicin.<br>Palmer-plantar erythrodysesthesia is more prominent. Educate patients to apply moisturizer proactively and wear loose-fitting shoes and socks.<br>Do not substitute for doxorubicin.<br>Do not use an in-line filter.<br>(Baxter Healthcare, 2019) |
|                                                        |                     | Epirubicin (Ellence®)          | IV    | Breast cancer                                                     | Dose-limiting toxicities: myelosuppression, cardiotoxicity<br>Nausea, vomiting, mucositis, diarrhea, alopecia, amenorrhea, infection, hyperuricemia, radiation recall, flushing, red-colored urine                                                         | The drug is red in color.<br>Epirubicin is a vesicant; extravasation can result in severe tissue injury.<br>Infuse into the side port of a free-flowing IV.<br>Do not use if baseline ANC is < 1,500/mm <sup>3</sup> .<br>Consider dose reduction in patients with hepatic and severe renal impairment (SCr > 5 mg/dl).<br>Cumulative dosing should not exceed 900 mg/m <sup>2</sup> .<br>Evaluate cardiac ejection fraction before starting epirubicin therapy.<br>(Pfizer, 2020b)                                                                         |
|                                                        |                     | Idarubicin (Idamycin®)         | IV    | AML                                                               | Dose-limiting toxicities: myelosuppression, cardiomyopathy<br>Hyperuricemia, nausea, vomiting, alopecia, vein itching, radiation recall, rash, mucositis, diarrhea, severe enterocolitis with perforation, red-colored urine                               | The drug is red-orange in color.<br>Idarubicin is a vesicant; extravasation can result in severe tissue injury. Inject slowly over 10–15 minutes into free-flowing side-arm infusion.<br>It is recommended not to exceed a lifetime maximum dose of > 150 mg/m <sup>2</sup> .<br>Local reactions (hives at the injection site) may occur.<br>Consider dose reduction in patients with renal or hepatic impairment.<br>(Pfizer, 2015)                                                                                                                        |

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**TABLE 6-1.** Chemotherapy Agents (*Continued*)

| Classification                                         | Mechanism of Action                                                                                                  | Drug                                           | Route                  | Indications                                                                                                                                                                                                                                                                                                                   | Side Effects                                                                                                                                                                                                                                                            | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|--------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|------------------------------------------------|------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Antitumor antibiotics: anthracyclines ( <i>Cont.</i> ) |                                                                                                                      | Mitoxantrone                                   | IV                     | Leukemia<br>Multiple sclerosis<br>Prostate cancer                                                                                                                                                                                                                                                                             | Dose-limiting toxicities: myelosuppression, cardiotoxicity (risk increased if patients were treated with other cardiotoxic drugs)<br>Nausea, vomiting, mucositis, alopecia, fever, weakness, hyperuricemia, amenorrhea, blue-green-colored urine, bluish skin or sclera | Mitoxantrone is fatal if given via routes other than IV.<br>The drug is blue in color.<br>Mitoxantrone has vesicant potential.<br>The risk of cardiotoxicity with mitoxantrone is less than that with doxorubicin, but prior anthracycline use, chest irradiation, or cardiac disease increases the risk.<br>Prior to beginning therapy, evaluate patients for cardiac signs and symptoms, including obtaining multigated acquisition scan, baseline left ventricular ejection fraction, and electrocardiogram.<br>It is recommended not to exceed a lifetime maximum dose of 140 mg/m <sup>2</sup> .<br>Mitoxantrone should not be used in patients with hepatic impairment.<br>(Fresenius Kabi USA, 2016d) |
|                                                        |                                                                                                                      | Valrubicin (Valstar®)                          | Intravesical           | Bladder cancer in situ refractory to bacillus Calmette-Guérin                                                                                                                                                                                                                                                                 | Dysuria, bladder spasm and irritation, urinary incontinence, leukopenia, hyperglycemia; drug may turn the urine red.                                                                                                                                                    | Administer via intravesical route only.<br>Do not use in pediatric patients.<br>Valrubicin is a vesicant; extravasation can result in severe tissue injury if bladder perforation occurs.<br>Use a non-PVC, non-DEHP containing tubing.<br>(Endo Pharmaceuticals Solutions, 2019)                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Miscellaneous                                          | Induces cytodifferentiation and decreased proliferation of acute promyelocytic leukemia cells in culture and in vivo | All-trans-retinoic acid (tretinoin, Vesanoid®) | PO, topical as a cream | Induction of remission in patients with acute promyelocytic leukemia characterized by the presence of t(15;17) translocation and/or the presence of <i>PML-RARA</i> fusion gene who are refractory to, or who have relapsed from, anthracycline chemotherapy, or for whom anthracycline-based chemotherapy is contraindicated | Headache, fever, dry skin, bone pain, nausea, vomiting, rash, pruritus, mouth sores, skin and oral membrane dryness, flu-like symptoms, abdominal pain, diarrhea, constipation, leukocytosis, differentiation, bleeding                                                 | PO: Patients should take with food.<br>Confirm negative pregnancy test in females within 1 week of starting treatment.<br>Instruct patients to use two forms of contraception during therapy and for 1 month following discontinuation of therapy.<br>(Roche Laboratories, 2013)                                                                                                                                                                                                                                                                                                                                                                                                                             |

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**TABLE 6-1.** Chemotherapy Agents (*Continued*)

| Classification                    | Mechanism of Action                                                                                                                                                             | Drug                                                 | Route | Indications                                                                                                                                      | Side Effects                                                                                                                                                                                                        | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|-----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------|-------|--------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Miscellaneous<br>( <i>Cont.</i> ) | Causes DNA fragmentation and morphologic changes characteristic of apoptosis in NB4 cells and degrades the chimeric promyelocytic leukemia/retinoic acid receptor-alpha protein | Arsenic trioxide (Trisenox®)                         | IV    | Acute promyelocytic leukemia                                                                                                                     | Fatigue, prolonged QT interval, acute promyelocytic leukemia differentiation syndrome, leukocytosis, headache, nausea, vomiting, diarrhea, abdominal pain, fever, dermatitis, cough, dyspnea, peripheral neuropathy | Use with caution with other agents that prolong QT/QTc interval. Obtain baseline electrocardiogram prior to therapy. Ensure QTc interval < 500 ms prior to infusion. QTc intervals should be measured periodically during therapy (e.g., weekly).<br>Use with caution in patients with renal impairment.<br>Monitor electrolytes during therapy. Maintain serum potassium > 4 mEq/L and magnesium > 1.8 mg/dl.<br>Renal or hepatic impairment may increase toxicity risk.<br>Administer over 1–2 hours (may be extended up to 4 hours if acute vasomotor reactions are observed).<br>(Teva Pharmaceuticals, 2016) |
|                                   | Depletes plasma asparagine, leading to leukemic cell death                                                                                                                      | Asparaginase <i>Erwinia chrysanthemi</i> (Erwinaze®) | IM    | ALL                                                                                                                                              | Hypersensitivity reaction (including anaphylaxis), pancreatitis, glucose intolerance, thrombosis, abdominal pain, diarrhea                                                                                          | Keep medications to treat anaphylaxis at the bedside.<br>Limit the volume of reconstituted asparaginase at a single injection site to 2 ml; if the reconstituted dose is > 2 ml, use multiple injection sites.<br>(Porton Biopharma, 2020)                                                                                                                                                                                                                                                                                                                                                                        |
|                                   | Inhibits growth phase of microtubules, arresting cell cycle at G <sub>2</sub> /M phase                                                                                          | Eribulin (Halaven®)                                  | IV    | Metastatic breast cancer<br>Unresectable or metastatic liposarcoma                                                                               | Dose-limiting toxicities: neutropenia, peripheral neuropathy<br>Fatigue, alopecia, nausea, constipation, anemia, QTc prolongation                                                                                   | Monitor electrolytes, electrocardiogram, and renal and liver function tests. Initiate at lower doses with hepatic or renal insufficiency.<br>Eribulin is not compatible with D <sub>5</sub> W.<br>(Eisai, 2021)                                                                                                                                                                                                                                                                                                                                                                                                   |
|                                   | Acts in S phase as an antimetabolite                                                                                                                                            | Hydroxyurea (Hydrea®, Mylo-cel®)                     | PO    | CML<br>Squamous cell cancer of the head and neck in combination with chemoradiation<br>Off-label use in acute leukemias, and sickle cell disease | Dose-limiting toxicity: myelosuppression<br>Vasculitic toxicities, macrocytosis, diarrhea, renal failure, mucositis, fever, hyperuricemia, rash, second malignancies                                                | Do not open capsules.<br>Monitor blood counts weekly and adjust dose for myelosuppression accordingly.<br>Patients should avoid live vaccines.<br>Patients should be educated to use sunscreen to avoid skin toxicity.<br>(Bristol-Myers Squibb, 2017c)                                                                                                                                                                                                                                                                                                                                                           |

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**TABLE 6-1.** Chemotherapy Agents (*Continued*)

| Classification                    | Mechanism of Action                                                                                                                                            | Drug                                 | Route | Indications                                                                                                    | Side Effects                                                                                                                                                                                    | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|-------|----------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Miscellaneous<br>( <i>Cont.</i> ) | Semisynthetic analog of epothilone B; binds to beta-tubulin on microtubules, leading to cell death by blocking cells in the M phase of the cell division cycle | Ixabepilone (Ixempra®)               | IV    | Metastatic or locally advanced breast cancer                                                                   | Dose-limiting toxicities: peripheral sensory neuropathy, myelosuppression, hypersensitivity reaction<br>Fatigue, myalgia, alopecia, nausea, vomiting, mucositis, diarrhea, musculoskeletal pain | Administer IV over 3 hours. Use non-PVC, non-DEHP bags and tubing; the solution is only stable for 6 hours.<br>Administer through a 0.2- to 1.2-micron in-line filter.<br>The drug is contraindicated in combination with capecitabine if bilirubin > 1 × ULN or aspartate aminotransferase or alanine aminotransferase > 2.5 × ULN. Patients may still receive monotherapy ixabepilone.<br>CYP3A4 inhibitors may increase ixabepilone concentration, and CYP3A4 inducers may decrease ixabepilone concentration. Avoid St. John's wort.<br>Premedicate with diphenhydramine (50 mg PO) and ranitidine (150–300 mg PO) 1 hour prior to dose to decrease the risk of hypersensitivity reaction.<br>(R-Pharm US, 2016) |
|                                   | Inhibits adrenal steroid production                                                                                                                            | Mitotane (Lysodren®)                 | PO    | Adrenocortical cancer                                                                                          | CNS toxicity, adrenal insufficiency/crisis, ovarian macrocysts in premenopausal women, anorexia, nausea, vomiting, mucositis, lethargy, dizziness or vertigo, rash                              | Monitor prothrombin time/international normalized ratio closely in patients on warfarin therapy.<br>Adrenal steroid replacement is indicated. Consider dose reduction in patients with renal or hepatic impairment.<br>(Bristol-Myers Squibb, 2017d)                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|                                   | Inhibits protein synthesis and is independent of direct BCR-ABL1 binding                                                                                       | Omacetaxine mepesuccinate (Synribo®) | SC    | CML in chronic or accelerated phase with resistance and/or intolerance to 2 or more tyrosine kinase inhibitors | Dose-limiting toxicity: myelosuppression<br>Thrombocytopenia with bleeding risk, hyperglycemia, nausea, vomiting, diarrhea, alopecia, fatigue                                                   | Monitor patients for bleeding. Rotate injection sites.<br>(Teva Pharmaceuticals, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

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**TABLE 6-1.** Chemotherapy Agents (*Continued*)

| Classification                    | Mechanism of Action                                                                 | Drug                     | Route                             | Indications                         | Side Effects                                                                                                                                                                                                             | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|-----------------------------------|-------------------------------------------------------------------------------------|--------------------------|-----------------------------------|-------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Miscellaneous<br>( <i>Cont.</i> ) | Depletes plasma asparagine, leading to leukemic cell death                          | Pegaspargase (Oncaspar®) | IM, IV                            | ALL                                 | Pancreatitis, thrombosis, glucose intolerance, coagulopathy, hepatotoxicity, allergic reactions (including anaphylaxis)                                                                                                  | Sometimes patients can be premedicated with acetaminophen, antihistamine, diphenhydramine, and corticosteroid (hydrocortisone). Refer to specific protocol.<br>Dosing is different based on the patient's age. For patients younger than 21 years: 2,500 unit/m <sup>2</sup> ; for patients older than 21 years: 2,000 units/m <sup>2</sup><br>When given IM, the maximum volume per injection site is 2 ml.<br>When given via IV, administer over 1–2 hours.<br>(Servier Pharmaceuticals, 2020)                                                                                                                                                  |
|                                   | May inhibit protein, RNA, and DNA synthesis                                         | Procarbazine (Matulane®) | PO                                | HL                                  | Dose-limiting toxicity: myelosuppression<br>Nausea, vomiting, hepatic dysfunction                                                                                                                                        | Patients should avoid foods high in tyramine, such as aged cheeses, air-dried or cured meats, fava or broad bean pods, tap/draft beer, wine (> 120 ml), vermouth, marmite concentrate, sauerkraut, and soy sauce and other soybean condiments because procarbazine inhibits monoamine oxidase.<br>Patients should avoid alcohol for the possibility of a disulfiram-like reaction.<br>(Sigma-Tau Pharmaceuticals, 2016)                                                                                                                                                                                                                           |
| Nitrosoureas                      | Breaks DNA helix, interfering with DNA replication; crosses the blood–brain barrier | Carmustine (BiCNU®)      | Implantation (Gliadel® wafer), IV | CNS tumors<br>Off-label use in HSCT | Dose-limiting toxicities: myelosuppression, pulmonary toxicity<br>Nausea, vomiting, renal toxicity<br>Gliadel-specific toxicities: seizures, intracranial hypertension, meningitis, impaired neurosurgical wound healing | Nadir occurs 4–6 weeks after start of therapy. Because of delayed toxicity, successive treatments usually are given no more frequently than once every 6–8 weeks.<br>Rapid infusion may cause burning along the vein and flushing of the skin (infuse over at least 2 hours).<br>Long-term therapy can result in irreversible pulmonary fibrosis, which may present as an insidious cough and dyspnea or sudden respiratory failure.<br>Use non-PVC, non-DEHP bags and tubing. The cumulative dose of 1,400 mg/m <sup>2</sup> should not be exceeded because of pulmonary toxicity.<br>(Arbor Pharmaceuticals, 2018; Bristol-Myers Squibb, 2017a) |

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**TABLE 6-1.** Chemotherapy Agents (*Continued*)

| Classification                    | Mechanism of Action                                                                    | Drug                       | Route | Indications                                     | Side Effects                                                                                                                                                                                                                                    | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|-----------------------------------|----------------------------------------------------------------------------------------|----------------------------|-------|-------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nitrosoureas<br>( <i>Cont.</i> )  |                                                                                        | Lomustine<br>(Gleostine®)  | PO    | Brain tumors<br>CNS tumors<br>HL                | Dose-limiting toxicity:<br>myelosuppression<br>(delayed, dose related,<br>cumulative)<br>Pulmonary toxicity, sec-<br>ond malignancies, hep-<br>atotoxicity, nephrotox-<br>icity, nausea, vomiting,<br>alopecia, fatigue, visual<br>disturbances | Because of delayed myelosuppression,<br>do not repeat the dose more than once<br>every 6 weeks. Only 1 dose should be<br>dispensed per treatment cycle.<br>Patients should take on an empty stomach.<br>Monitor pulmonary, liver, and renal function.<br>(NextSource Biotechnology, 2016)                                                                                                                                                                                                                                                                                                                                                  |
|                                   |                                                                                        | Streptozocin<br>(Zanosar®) | IV    | Metastatic islet-cell pan-<br>creatic carcinoma | Dose-limiting toxicity:<br>renal toxicity<br>Myelosuppression, nau-<br>sea, vomiting, hypogly-<br>cemia, proteinuria, hep-<br>atotoxicity, confusion,<br>lethargy, depression                                                                   | Streptozocin is an irritant.<br>Nephrotoxicity may be dose limiting.<br>The drug may alter glucose metabolism in<br>some patients.<br>(Teva Parenteral Medicines, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Plant alkaloids:<br>camptothecins | Acts in S phase; inhib-<br>its topoisomerase I;<br>causes double-strand<br>DNA changes | Irinotecan                 | IV    | Metastatic colorectal<br>cancer                 | Dose-limiting toxicity:<br>diarrhea<br>Myelosuppression, hyper-<br>sensitivity reaction, alo-<br>pecia, fever, nausea,<br>vomiting                                                                                                              | Irinotecan is an irritant; exfoliative dermati-<br>tis may occur.<br>This drug can cause early and late diarrhea,<br>which can be dose limiting. Early diarrhea<br>can occur within 24 hours of administra-<br>tion and generally is cholinergic.<br>Prophylactic atropine 0.25–1 mg IV prior<br>to irinotecan can help relieve immedi-<br>ate stomach discomfort (cramping). It can<br>also help with flushing that can occur with<br>the infusion. An additional dose of atro-<br>pine can be given if needed.<br>For moderate emetic potential with delayed<br>nausea, ensure an appropriate antiemetic<br>regimen.<br>(Hospira, 2020b) |

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**TABLE 6-1.** Chemotherapy Agents (*Continued*)

| Classification                                  | Mechanism of Action                                                                                                                                            | Drug                                                                     | Route  | Indications                                                                         | Side Effects                                                                                                             | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|--------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Plant alkaloids: camptothecins ( <i>Cont.</i> ) | Inhibits topoisomerase I                                                                                                                                       | Irinotecan liposomal (Onivyde®)                                          | IV     | Relapsed/refractory metastatic adenocarcinoma of the pancreas                       | Interstitial lung disease, diarrhea, fatigue, nausea, vomiting, stomatitis, pyrexia                                      | Administer 70 mg/m <sup>2</sup> IV over 90 minutes every 2 weeks in combination with 5-FU and leucovorin. The recommended dose for patients homozygous for UGT1A1*28 is 50 mg/m <sup>2</sup> every 2 weeks. Premedicate with a corticosteroid and an antiemetic 30 minutes prior to administration. Ensure patients have anti-diarrheal medication to use if diarrhea occurs. (Ipsen Biopharmaceuticals, 2020)                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|                                                 |                                                                                                                                                                | Topotecan (Hycamtin®)                                                    | IV, PO | Cervical cancer<br>Metastatic ovarian cancer<br>Small cell lung cancer              | Dose-limiting toxicity: myelosuppression<br>Diarrhea, alopecia, nausea, vomiting, fatigue, interstitial lung disease     | Do not administer to patients with baseline ANC < 1,500/mm <sup>3</sup> or platelets <100,000/mm <sup>3</sup> . Consider dose reduction in patients with renal impairment. (Novartis Pharmaceuticals, 2018)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Plant alkaloids: epipodophylotoxins             | Induces irreversible blockade of cells in premitotic phases of cell cycle (late G <sub>2</sub> and S phases); interferes with topoisomerase II enzyme reaction | Etoposide (VP-16, Toposar®, VePesid®); etoposide phosphate (Etoposphos®) | IV, PO | Testicular cancer<br>Small cell lung cancer<br>Off-label uses in lymphomas and HSCT | Dose-limiting toxicity: myelosuppression<br>Hypersensitivity reaction, nausea, vomiting, alopecia, anorexia, hypotension | Do not administer via rapid IV infusion or IV push. Infuse over at least 30 minutes to avoid hypotension. Infusion time will be determined on final volume (30 minutes to 4 hours). Stability varies based on concentration. Drug may crystallize if concentration > 1 mg/ml. If patients have an allergic reaction to etoposide, premedicate with diphenhydramine. Consider dose reduction in patients with renal impairment. When used for HSCT, doses are very high. The undiluted drug will be used. The risk of hypotension increases due to the amount of alcohol in liquid etoposide. PO etoposide causes more nausea; ensure patients have scheduled antiemetics prior to each dose. Daily doses > 200 mg should be given in divided doses (twice daily) for tolerability. (Bristol-Myers Squibb, 2017b; Mylan Pharmaceuticals, 2016; Teva Parenteral Medicines, 2018) |

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**TABLE 6-1.** Chemotherapy Agents (*Continued*)

| Classification                                       | Mechanism of Action                                                                         | Drug                   | Route | Indications                                                                                                                            | Side Effects                                                                                                                                        | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|------------------------------------------------------|---------------------------------------------------------------------------------------------|------------------------|-------|----------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Plant alkaloids: epipodophylotoxins ( <i>Cont.</i> ) |                                                                                             | Teniposide             | IV    | Induction therapy in pediatric ALL                                                                                                     | Dose-limiting toxicity: myelosuppression<br>Hypersensitivity reaction, anaphylaxis, nausea, vomiting, mucositis, diarrhea, alopecia                 | The drug may cause an allergic reaction. Do not administer via rapid infusion. Infuse over 30–60 minutes to avoid hypotension. Use non-PVC, non-DEHP bags and tubing. The drug is contraindicated in patients with a history of reactions to teniposide or other drugs formulated in polyoxyl 35 castor oil (a solvent). Consider dose reduction in patients with renal or hepatic impairment. (WG Critical Care, 2015)                                                                                                                                                                                                                                                                       |
| Plant alkaloids: taxanes                             | Stabilizes microtubules, inhibiting cell division; effective in G <sub>2</sub> and M phases | Cabazitaxel (Jevtana®) | IV    | Hormone-refractory metastatic prostate cancer                                                                                          | Hypersensitivity reaction, myelosuppression, fatigue, diarrhea, nausea, vomiting, peripheral neuropathy                                             | Withhold dose for ANC < 1,500/mm <sup>3</sup> . Severe myelosuppression can occur; consider primary prophylaxis with granulocyte-colony-stimulating factor. Premedicate with the following to prevent hypersensitivity reaction, including anaphylaxis, at least 30 minutes before treatment: IV diphenhydramine 25 mg, dexamethasone 8 mg, and ranitidine 50 mg. Infuse over 1 hour, through a 0.2-micron in-line filter. Use non-PVC bags and tubing. Do not use in patients with severe hepatic impairment (total bilirubin > 3 × ULN). Dose adjustment is needed for mildly elevated total bilirubin or aspartate aminotransferase/alanine aminotransferase. (Sanofi-Aventis U.S., 2021a) |
|                                                      |                                                                                             | Docetaxel (Taxotere®)  | IV    | Breast cancer<br>Gastric adenocarcinoma<br>Hormone-refractory prostate cancer<br>NSCLC<br>Squamous cell carcinoma of the head and neck | Myelosuppression, febrile neutropenia, hypersensitivity reaction, fluid retention, alopecia, skin and nail changes, nausea, vomiting, neurotoxicity | Premedicate with the following to reduce the severity of hypersensitivity reaction and fluid retention: dexamethasone 8 mg PO twice daily for 3 days, beginning 1 day prior to docetaxel treatment. Docetaxel extravasation may cause local pain, edema, erythema, and hyperpigmentation at the infusion site. Do not administer if bilirubin > ULN or aspartate aminotransferase and/or alanine aminotransferase > 1.5 × ULN with alkaline phosphatase > 2.5 × ULN.                                                                                                                                                                                                                          |

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**TABLE 6-1.** Chemotherapy Agents (*Continued*)

| Classification                               | Mechanism of Action | Drug                                         | Route                | Indications                                                                                                                                                                                                                              | Side Effects                                                                                                                                                                                                                    | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|----------------------------------------------|---------------------|----------------------------------------------|----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Plant alkaloids:<br>taxanes ( <i>Cont.</i> ) |                     | Docetaxel<br>(Taxotere®)<br>( <i>Cont.</i> ) |                      |                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                 | Withhold dose for ANC < 1,500/mm <sup>3</sup> .<br>Use non-PVC, non-DEHP bags and tubing to administer docetaxel.<br>Infuse over 1 hour.<br>A cold cap may prevent or reduce alopecia in certain settings; check with specific protocol.<br>(Sanofi-Aventis U.S., 2021b)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|                                              |                     | Paclitaxel                                   | IV, intra-peritoneal | AIDS-related Kaposi sarcoma<br>Breast cancer<br>Metastatic adenocarcinoma of the pancreas<br>Metastatic breast cancer<br>NSCLC<br>Ovarian cancer<br>Off-label uses for various solid tumors, including gastric and head and neck cancers | Dose-limiting toxicities: myelosuppression, sensory neuropathy<br>Hypersensitivity reaction (dyspnea, hypotension, angioedema, urticaria), sepsis, pneumonitis, alopecia, anemia, myalgia/arthritis, nausea, vomiting, diarrhea | Paclitaxel is an irritant and potential vesicant. Extravasation may lead to local pain, edema, and erythema at the infusion site. Paclitaxel is contraindicated in patients with a history of reactions to paclitaxel or other drugs formulated in polyoxyl 35 castor oil (a solvent). Patients should be premedicated to minimize reaction risk: Dexamethasone, diphenhydramine, and ranitidine/famotidine are given prior to infusion. Premedication dosages and frequency may vary per specific regimens. Reactions occur more frequently with the first or second dose.<br>Monitor for peripheral neuropathy related to the cumulative dose received, and apply dose reduction when necessary. Monitor CBC and hold paclitaxel if ANC < 1,500/mm <sup>3</sup> . Drug should not be given to patients with AIDS-related Kaposi sarcoma if baseline neutrophil count < 1,000/mm <sup>3</sup> .<br>Filter paclitaxel with a 0.2-micron in-line filter.<br>Use non-PVC, non-DEHP bags and tubing to administer paclitaxel.<br>To prevent severe myelosuppression, administer paclitaxel before platinum-containing drugs.<br>A cold cap may prevent or reduce alopecia in certain settings; check with specific protocol.<br>(Hospira, 2021a) |

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**TABLE 6-1.** Chemotherapy Agents (*Continued*)

| Classification                               | Mechanism of Action                                                                                                                                                | Drug                                                                                         | Route | Indications                                                                                                                                     | Side Effects                                                                                                                                                                          | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|----------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|-------|-------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Plant alkaloids:<br>taxanes ( <i>Cont.</i> ) |                                                                                                                                                                    | Paclitaxel<br>protein-bound<br>particles;<br>albumin-bound<br>(Nab-paclitaxel;<br>Abraxane®) | IV    | HL<br>Metastatic adenocarcinoma of the pancreas<br>Metastatic breast cancer<br>Neuroblastoma<br>NHL<br>NSCLC<br>Rhabdomyosarcoma<br>Wilms tumor | Dose-limiting toxicities:<br>myelosuppression, sensory neuropathy<br>Sepsis, pneumonitis, hypersensitivity reaction, alopecia, anemia, myalgia/arthralgia, nausea, vomiting, diarrhea | The solution usually takes approximately 20 minutes to prepare in the pharmacy due to the slow dissolution of the powder. Premedication is generally not required. Withhold dose for grade 3–4 peripheral neuropathy; resume only with grade 1 or complete resolution. (Celgene, 2022a)                                                                                                                                                                                                                                                  |
| Plant alkaloids:<br>vinca alkaloids          | Interacts with tubulin and disrupts microtubule function, particularly of microtubules comprising the mitotic spindle apparatus, directly causing metaphase arrest | Vinblastine                                                                                  | IV    | Breast cancer<br>HL<br>Histiocytosis<br>Kaposi sarcoma<br>Mycosis fungoides<br>NHL<br>Testicular cancer                                         | Dose-limiting toxicities:<br>myelosuppression, constipation, neurotoxicity, peripheral neuropathy, jaw pain<br>Alopecia<br>Toxicities may be enhanced with hepatic insufficiency.     | The drug is fatal if given via routes other than IV. Vinblastine is a vesicant; extravasation can result in severe tissue injury. Administer via a minibag through the side port of a free-flowing IV. Generally, neurotoxicity occurs less frequently with vinblastine than with vincristine; however, it is rare and usually reversible. (Fresenius Kabi USA, 2016e)                                                                                                                                                                   |
|                                              |                                                                                                                                                                    | Vincristine                                                                                  | IV    | ALL<br>HL<br>NHL<br>Neuroblastoma<br>Wilms tumor<br>Rhabdomyosarcoma                                                                            | Dose-limiting toxicity:<br>neurotoxicity<br>Alopecia, peripheral neuropathy, constipation, paralytic ileus, renal toxicity, hepatotoxicity, hypersensitivity reaction                 | The drug is fatal if given via routes other than IV. Vincristine is a vesicant; extravasation can result in severe tissue injury. Administer via a minibag through the side port of a free-flowing IV. Neurotoxicity is cumulative; conduct a neurologic evaluation before each dose. Withhold dose if severe paresthesia, motor weakness, or other abnormality develops. Reduce dose in the presence of significant liver disease. Stool softeners and/or a stimulant laxative may help to prevent severe constipation. (Hospira, 2013) |

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**TABLE 6-1.** Chemotherapy Agents (*Continued*)

| Classification                                          | Mechanism of Action                                                                               | Drug                                                    | Route | Indications                                                                                                                                   | Side Effects                                                                                                                                                                                                                                          | Nursing Considerations                                                                                                                                                                                                                                                                                                                               |
|---------------------------------------------------------|---------------------------------------------------------------------------------------------------|---------------------------------------------------------|-------|-----------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Plant alkaloids:<br>vinca alkaloids<br>( <i>Cont.</i> ) | The liposomal form increases the drug's half-life, enhancing its cytotoxic effect in tumor cells. | Vincristine lipo-<br>somal (Marq-<br>ibo <sup>®</sup> ) | IV    | Philadelphia chromosome–<br>negative ALL in second<br>or greater relapse that<br>has progressed after 2 or<br>more antileukemic reg-<br>imens | Fatigue, nausea, pyrexia,<br>myelosuppression,<br>peripheral neuropathy,<br>liver toxicity, constipa-<br>tion, embryo-fetal tox-<br>icity                                                                                                             | The drug is fatal if given via routes other<br>than IV.<br>The solution takes 90 minutes to prepare in<br>the pharmacy.<br>Vincristine liposomal is a vesicant; extrava-<br>sation can result in severe tissue injury.<br>Administer over 1 hour every 7 days.<br>(Talon Therapeutics, 2016)                                                         |
|                                                         |                                                                                                   | Vinorelbine<br>(Navelbine <sup>®</sup> )                | IV    | NSCLC<br>Off-label use in breast<br>cancer                                                                                                    | Dose-limiting toxicities:<br>myelosuppression, hep-<br>atotoxicity, severe con-<br>stipation and bowel<br>obstruction, neurotoxic-<br>ity (peripheral neuropa-<br>thy), pulmonary toxicity,<br>respiratory failure<br>Nausea, vomiting, alo-<br>pecia | The drug is fatal if given via routes other<br>than IV.<br>Vinorelbine is a vesicant. Extravasation can<br>result in severe tissue injury.<br>Administer via a minibag through the side<br>port of a free-flowing IV. After completion,<br>a flush with 75–125 ml of the solution may<br>minimize phlebitis.<br>(Pierre Fabre Pharmaceuticals, 2020) |

*Note.* For drugs listed as vesicants or irritants, refer to Chapter 13. Review package inserts for dosing and prescribing information.

ALL—acute lymphoblastic leukemia; AML—acute myeloid leukemia; ANC—absolute neutrophil count; AUC—area under the plasma concentration versus-time curve; CBC—complete blood count; CLL—chronic lymphocyte leukemia; CML—chronic myeloid leukemia; CNS—central nervous system; CrCl—creatinine clearance; CYP—cytochrome P450; DEHP—di(2-ethylhexyl) phthalate; D<sub>5</sub>W—5% dextrose in water; 5-FU—5-fluorouracil; FDA—U.S. Food and Drug Administration; GI—gastrointestinal; G<sub>2</sub>—gap 2; HL—Hodgkin lymphoma; HSCT—hematopoietic stem cell transplantation; IM—intramuscular; IT—intrathecal; IV—intravenous; M—mitosis; ms—millisecond; NHL—non-Hodgkin lymphoma; NS—normal saline; NSCLC—non-small cell lung cancer; PO—by mouth; PVC—polyvinyl chloride; QTc—QT interval corrected; S—synthesis; SC—subcutaneous; Scr—serum creatinine; TLS—tumor lysis syndrome; UGT—uridine diphosphate-glucuronosyltransferase; ULN—upper limit of normal

## 2. Antimetabolites

- Antimetabolites block DNA and RNA growth by interfering with enzymes. For example, antifolates interfere with folate, which is necessary for healthy cellular metabolism.
- Antimetabolites are often divided into folate analogs, purine analogs, adenosine analogs, pyrimidine analogs, and substituted ureas.
- Tumors with a high growth rate or a high percentage of cells in the S phase are the most susceptible to antimetabolites (Vlcek, 2022). Healthy cells with high division rates, such as gastrointestinal mucosal and bone marrow cells, are sensitive to antimetabolites, resulting in mucositis, diarrhea, and myelosuppression.
- Examples include capecitabine, cytarabine, 5-fluorouracil, gemcitabine, and methotrexate.

## 3. Antitumor antibiotics (Vlcek, 2022)

- Antitumor antibiotics interfere with the synthesis of DNA and RNA through various mechanisms.
- Myelosuppression, gastrointestinal toxicities, and alopecia are common.
- A number of these agents are cardiotoxic or pulmonary toxic.
- Examples include doxorubicin, bleomycin, epirubicin, mitoxantrone, and dactinomycin.

## 4. Miscellaneous agents

- The drugs in this category have a unique mechanism of action and side effect profile. They cannot be grouped with other chemotherapy agents.
- Examples include asparaginase, arsenic, and vorinostat.
  - Asparaginase is an enzyme derived from bacteria (*Escherichia coli* or *Erwinia chrysanthemi*) that depletes circulating levels of asparagine, resulting in cell death.
  - Arsenic is a differentiating agent that causes fragmented changes in DNA, leading to apoptosis. It inhibits the self-renewal of leukemia cells due to free radical formation (Vlcek, 2022).

## 5. Nitrosoureas

- Nitrosoureas are a distinct group of drugs that can cross the blood–brain barrier (high lipid solubility). They are sometimes categorized with alkylating agents.
- Nitrosoureas cause breakage in the DNA helix strand, interfering with DNA replication and ultimately resulting in cell death.
- Dose-limiting toxicities include bone marrow suppression, gastrointestinal toxicities, and organ-specific toxicities (e.g., renal and hepatic, dependent on drug and dose).

d) Other effects include carcinogenic and mutagenic effects and impaired fertility.

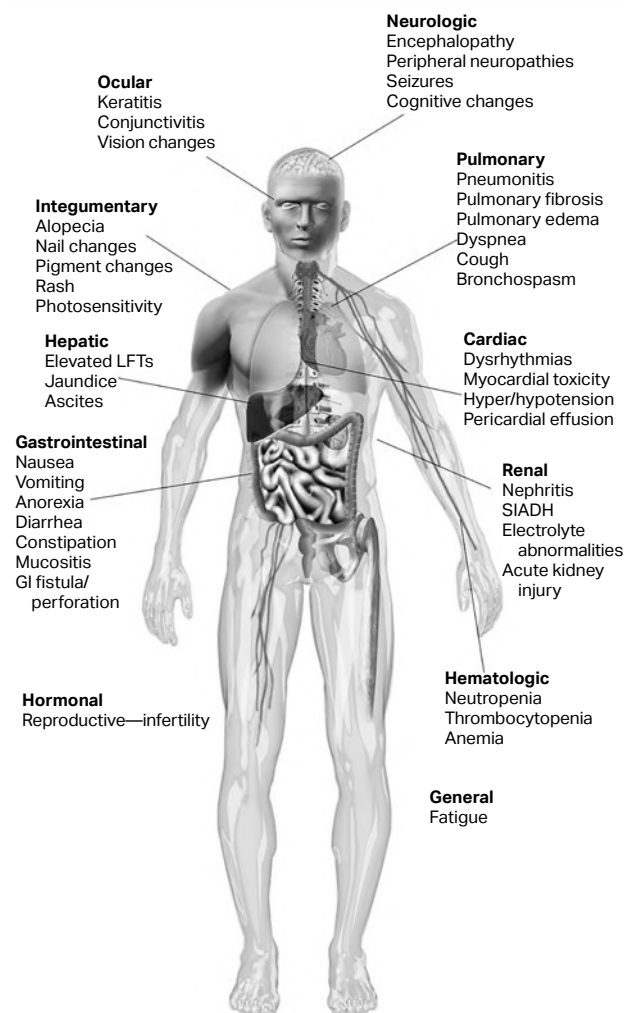
e) Examples include carmustine, lomustine, and streptozocin.

## 6. Plant alkaloids

## a) Camptothecins

- Camptothecins are semisynthetic analogs of the alkaloid camptothecin obtained from the Chinese ornamental tree *Camptotheca acuminata*.
- They target topoisomerase I, an enzyme necessary for DNA synthesis, causing DNA damage and cell death.
- Diarrhea and myelosuppression are the most common dose-limiting toxicities.

**FIGURE 6-2.** Potential Side Effects and Toxicities of Chemotherapy by System



GI—gastrointestinal; LFTs—liver function tests; SIADH—syndrome of inappropriate antidiuretic hormone secretion

Note. Image courtesy of University of Texas MD Anderson Cancer Center. Used with permission.

- (4) Examples include irinotecan and topotecan.

b) Epipodophyllotoxins

- (1) Epipodophyllotoxins are an antimicrotubule agent derived from the plant *Podophyllum peltatum*, or mandrake.
- (2) They induce irreversible blockage of cells in the premitotic cell cycle phases (late G<sub>2</sub> and S) and interfere with topoisomerase II enzyme reaction.
- (3) Myelosuppression with a nadir of 10–14 days is a dose-limiting toxicity. Mild to moderate nausea, vomiting, mucositis, and alopecia also can occur with this class and are dose dependent.
- (4) These agents may also have carcinogenic and mutagenic effects.

c) Taxanes

- (1) Taxanes are semisynthetic derivatives of precursors from yew plants.
- (2) They stabilize microtubules, inhibiting cell division, and are effective in the G<sub>2</sub> and M phases.
- (3) Common side effects include infusion reactions, peripheral neuropathy, myelosuppression, arthralgias, and myalgias. Docetaxel is associated with edema and nail changes.

d) Vinca alkaloids

- (1) Vinca alkaloids are derived from the plant *Vinca rosea*, or periwinkle.
- (2) They depolymerize microtubules and destroy mitotic spindles.
- (3) Myelosuppression (except with vincristine) and neurologic and hepatic toxicities are common.
- (4) The drugs in this category are vesicants.
- (5) The drugs in this category are fatal if given into the central nervous system.

## D. Combination chemotherapy principles

### 1. Benefits

- a) Maximum cell kill within dose limits
- b) Broader coverage to overcome resistant cell lines

### 2. Drug selection for combination chemotherapy

- a) Are active as single agents
- b) Have differing mechanisms of action, making them synergistic
- c) Have differing dose-limiting toxicities to allow therapy doses to be tolerated
- d) Have differing patterns of resistance
- e) Should be used at the optimal schedule and dose
- f) Should be given at consistent intervals

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## CHAPTER 7

# Hormone Therapy

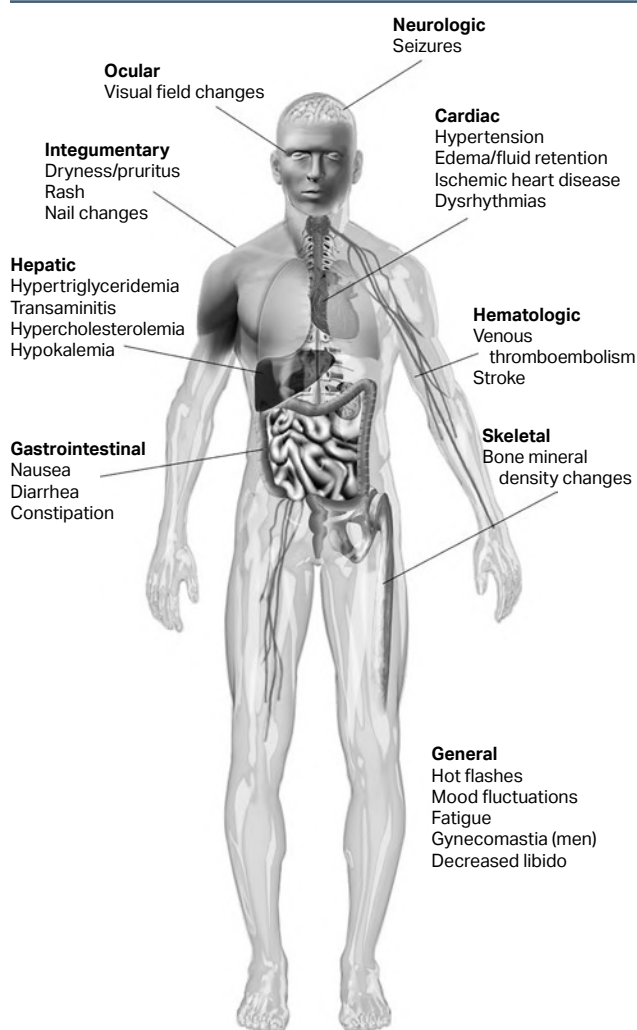
### A. Hormone therapy in the treatment of cancer

1. Hormone manipulation is used to treat many hormonally sensitive cancers. Although prostate and breast cancers are prime examples, endocrine treatment is also used for adrenal, thyroid, and androgen-sensitive salivary gland cancers.
2. Current endocrine treatments involve decreasing the levels of a specific hormone in the body by interfering with its release, blocking other hormones that trigger its production and release, blocking hormone receptors, or destroying the hormone entirely.
3. Although effective in prolonging survival, hormone treatments have side effects that may affect an individual's quality of life or be associated with physiologic changes that increase the risk for other health conditions.
4. This chapter will provide a brief overview of cancers treated with endocrine therapy, describe categories of hormones used in cancer treatment, identify associated side effects and health risks (see Figure 7-1), and discuss implications for nursing care. See Table 7-1 for additional drug-specific information.

### B. Cancers treated with hormone therapy

1. Prostate and breast cancer are the most commonly diagnosed cancers among men and women, respectively, and are the most common malignancies treated with hormone therapy. Although both cancers exist in a hormone milieu, differences exist in mechanisms and response to hormone therapy (National Comprehensive Cancer Network [NCCN], 2021a, 2022; Siegel et al., 2021).
2. Hormone therapy for specific cancers
  - a) Prostate cancer
    - (1) Androgens (e.g., testosterone, dihydrotestosterone) are hormones essential for reproductive function, secondary sexual characteristics, and muscle and bone growth in men (Zhou et al., 2018).
    - (2) Testosterone is synthesized in the testes and adrenal glands before being released into the circulation.

**FIGURE 7-1.** Potential Side Effects and Toxicities of Hormone Therapy by System



*Note.* Image courtesy of University of Texas MD Anderson Cancer Center. Used with permission.

**TABLE 7-1.** Hormone Therapy Agents

| Classification                                 | Drug                   | Route and Dosing                                                                         | Indications                                                                                                                | Side Effects                                                                                                                                                                                                                                                                                                           | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|------------------------------------------------|------------------------|------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Adrenolytics                                   | Mitotane (Lysodren®)   | 0.5–2 g PO daily, titrated up every 1–2 weeks to serum concentrations between 14–20 mg/L | Adrenal cancer                                                                                                             | Anorexia, nausea, diarrhea, transaminitis, hypercholesterolemia, hypothyroidism, glucocorticoid excess                                                                                                                                                                                                                 | Administer in 3–4 divided daily doses. Cerebellar ataxia and other neurologic symptoms may develop with concentrations > 20 mg/L. (Corden Pharma Latina, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Androgen receptor inhibitors and antiandrogens | Darolutamide (Nubeqa™) | 300 mg PO twice daily                                                                    | Nonmetastatic, castration-resistant prostate cancer                                                                        | Pain in extremities, rash, fatigue, renal toxicity and hepatotoxicity, neutropenia                                                                                                                                                                                                                                     | Tablets should be swallowed whole and taken with food. If patients miss a dose, it should be taken as soon as remembered and should not be doubled. Patients should concomitantly receive a gonadotropin-releasing hormone analog or should have had a bilateral orchiectomy. Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the final dose of darolutamide. Darolutamide may impair fertility in males of reproductive potential. The safety of darolutamide for female partners who are breastfeeding has not been established. Concomitant use with combined P-gp and strong or moderate CYP3A inducers or inhibitors should be avoided. Monitor patients more frequently for adverse reactions. Concomitant use with drugs that are BCRP substrates should be avoided when possible. Monitor patients more frequently for adverse reactions and consider a dose reduction of the BCRP substrate drug if use cannot be avoided. (Bayer HealthCare Pharmaceuticals, 2021) |
|                                                | Apalutamide (Erleada™) | 240 mg PO daily                                                                          | Prostate cancer<br>Nonmetastatic, castration-resistant prostate cancer<br>Metastatic, castration-sensitive prostate cancer | GI effects (nausea, diarrhea), fatigue, decreased appetite, seizures, falls or fracture, hypertension, rash, weight loss, arthralgia, peripheral edema<br>Adverse events, such as the potential for ischemic cardiovascular events, fractures, increased risk for falls in older adult patients, embryo-fetal toxicity | Patients should receive apalutamide with a gonadotropin-releasing hormone analog concurrently or should have a bilateral orchiectomy. Men should be counseled not to donate sperm during treatment and for at least 3 months following the final dose of apalutamide. CYP–drug interactions are possible. Drug should be swallowed whole and may be taken with or without food. Monitor for signs and symptoms of ischemic heart disease. In the presence of ≥ grade 3 toxicity or intolerable side effects, withhold dose until symptoms improve to ≤ grade 1; once symptoms are controlled, resume drug at the same or a reduced dose.                                                                                                                                                                                                                                                                                                                                                                                                                              |

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**TABLE 7-1.** Hormone Therapy Agents (*Continued*)

| Classification                                                  | Drug                                    | Route and Dosing                                          | Indications                                                                                                 | Side Effects                                                                                                                                                                         | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                  |
|-----------------------------------------------------------------|-----------------------------------------|-----------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Androgen receptor inhibitors and antiandrogens ( <i>Cont.</i> ) | Apalutamide (Erleada™) ( <i>Cont.</i> ) |                                                           |                                                                                                             |                                                                                                                                                                                      | Patients should use contraception during treatment and for 3 months after the final dose if they have a female partner of reproductive potential. Concomitant use with sensitive substrates of CYP3A4, CYP2C19, CYP2C9, UGT, P-gp, BCRP, or OATP1B1 may lead to loss of activity of these medications and should be avoided. (Janssen Pharmaceutical Companies, 2020a)                                                  |
|                                                                 | Bicalutamide (Casodex®)                 | 50 mg PO daily                                            | Prostate cancer                                                                                             | Hepatotoxicity, GI effects (nausea, diarrhea, constipation), fatigue                                                                                                                 | Drug can be added to LHRH agonist or antagonist therapy after progression or used temporarily to prevent symptoms of tumor flare. Bicalutamide offers better tolerance and once-daily dosing compared to nilutamide and flutamide. CYP–drug interactions are possible. (AstraZeneca Pharmaceuticals, 2017)                                                                                                              |
|                                                                 | Enzalutamide (Xtandi®)                  | 160 mg PO daily                                           | Prostate cancer<br>Castration-resistant prostate cancer<br>Metastatic, castration-sensitive prostate cancer | GI effects (nausea, diarrhea, constipation), fatigue, seizures, decreased appetite, hot flashes, arthralgia, hypertension, dizziness, headache<br>Falls and fractures, hyperglycemia | Enzalutamide is a pure androgen receptor signaling inhibitor. Patients should receive enzalutamide with a gonadotropin-releasing hormone analog concurrently or should have previously undergone a bilateral orchiectomy. CYP–drug interactions are possible. Capsules should be swallowed whole and may be taken with or without food. Capsules should not be chewed, dissolved, or opened. (Astellas Pharma US, 2021) |
|                                                                 | Flutamide (Eulexin®)                    | 250 mg PO every 8 hours                                   | Prostate cancer                                                                                             | Hepatotoxicity, GI effects (nausea, diarrhea, constipation), fatigue                                                                                                                 | Drug can be added to LHRH agonist or antagonist therapy after progression or used temporarily to prevent symptoms of tumor flare. CYP–drug interactions are possible. (AA Pharma, 2019)                                                                                                                                                                                                                                 |
|                                                                 | Nilutamide (Nilandron®)                 | 300 mg PO daily for 30 days, then 150 mg daily thereafter | Prostate cancer                                                                                             | Hepatotoxicity, GI effects (nausea, diarrhea, constipation), fatigue, visual field changes, disulfiram-like reaction                                                                 | Drug can be added to LHRH agonist or antagonist therapy after progression or used temporarily to prevent symptoms of tumor flare. CYP–drug interactions are possible. (ANI Pharmaceuticals, 2015)                                                                                                                                                                                                                       |
| Aromatase inhibitors                                            | Anastrozole (Arimidex®)                 | 1 mg PO daily                                             | HR-positive breast cancer                                                                                   | Arthralgias and myalgias, decreased BMD, fatigue, hot flashes, CVD (hypertension, edema, ischemic heart disease), hypercholesterolemia, venous thromboembolism                       | If adverse effects are intolerable, another aromatase inhibitor may be given. Drug is used in postmenopausal patients or premenopausal patients with ovarian ablation. Breast cancer must be HR-positive. (ANI Pharmaceuticals, 2021)                                                                                                                                                                                   |

(Continued on next page)

**TABLE 7-1.** Hormone Therapy Agents (*Continued*)

| Classification                                                            | Drug                          | Route and Dosing                                                              | Indications               | Side Effects                                                                                                                                                   | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|---------------------------------------------------------------------------|-------------------------------|-------------------------------------------------------------------------------|---------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Aromatase inhibitors ( <i>Cont.</i> )                                     | Exemestane (Aromasin®)        | 25 mg PO daily                                                                | HR-positive breast cancer | Arthralgias and myalgias, decreased BMD, fatigue, hot flashes, CVD (hypertension, edema, ischemic heart disease), hypercholesterolemia, venous thromboembolism | If adverse effects are intolerable, another aromatase inhibitor may be given.<br>Drug is used in postmenopausal patients or premenopausal patients with ovarian ablation.<br>Breast cancer must be HR-positive.<br>(Pfizer, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                                                                           | Letrozole (Femara®)           | 2.5 mg PO daily                                                               | HR-positive breast cancer | Arthralgias and myalgias, decreased BMD, fatigue, hot flashes, CVD (hypertension, edema, ischemic heart disease), hypercholesterolemia, venous thromboembolism | If adverse effects are intolerable, another aromatase inhibitor may be given.<br>Drug is used in postmenopausal patients or premenopausal patients with ovarian ablation.<br>Breast cancer must be HR-positive.<br>(Novartis Pharmaceuticals, 2020)                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| CYP17 inhibitors                                                          | Abiraterone (Zytiga®; Yonsa®) | Zytiga: 1,000 mg PO daily<br>Yonsa: 500 mg PO daily                           | Prostate cancer           | Hypertension, fluid retention, hypokalemia, transaminitis, hypertriglyceridemia, fatigue                                                                       | CYP and P-gp drug interactions are possible.<br>Use with caution in patients with cardiovascular disease and hepatic impairment.<br>Zytiga and Yonsa should not be interchanged due to differences in dosing and total body exposure based on recent meal intake.<br>Zytiga-specific considerations: Administer with prednisone 5 mg twice daily to mitigate symptoms of mineralocorticoid excess.<br>Administer on an empty stomach.<br>Yonsa-specific considerations: Administer with methylprednisolone 4 mg twice daily to mitigate symptoms of mineralocorticoid excess.<br>The drug can be taken with or without food<br>(Janssen Pharmaceutical Companies, 2020b; Sun Pharmaceuticals, 2021) |
|                                                                           | Ketoconazole (Nizoral®)       | 400 mg PO 3 times daily                                                       | Prostate cancer           | Black box warnings: severe hepatotoxicity, QTc prolongation<br>Diarrhea, gynecomastia, fatigue, dizziness                                                      | Administer with soda or other acidic beverages for better absorption.<br>Administer with oral hydrocortisone 20 mg every morning and 10 mg every evening to simulate physiologic adrenocortical release.<br>CYP and P-gp drug interactions are possible.<br>(Janssen Pharmaceutical Companies, 2013)                                                                                                                                                                                                                                                                                                                                                                                                |
| Estrogen receptor antagonists/ selective estrogen receptor downregulators | Fulvestrant (Faslodex®)       | Loading: 500 mg IM days 1, 15, and 29<br>Maintenance: 500 mg IM every 4 weeks | HR-positive breast cancer | Injection site pain, hot flashes, musculoskeletal weakness                                                                                                     | Each dose is administered as two 250 mg (5 ml) injections over 1–2 minutes.<br>Breast cancer must be HR-positive.<br>(AstraZeneca Pharmaceuticals, 2020)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

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**TABLE 7-1.** Hormone Therapy Agents (*Continued*)

| Classification   | Drug                                 | Route and Dosing                                                                                                                                                                           | Indications                                  | Side Effects                                                                                                                                                                                                                                   | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                  |
|------------------|--------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| LHRH agonists    | Goserelin (Zoladex®)                 | 3.6 mg SC every 4 weeks<br>10.8 mg SC every 12 weeks (prostate only)                                                                                                                       | HR-positive breast cancer<br>Prostate cancer | Injection site pain, mood changes, hot flashes, decreased libido, musculoskeletal weakness, decreased BMD, CVD (QTc prolongation, heart failure), gynecomastia (men)                                                                           | Temporary tumor flare (bladder outlet obstruction, bone pain, neurologic symptoms) may occur within the first few weeks after the initial dose secondary to initial increases in estradiol or testosterone levels. Breast cancer must be HR-positive. (TerSera Therapeutics, 2020)                                                                                                                                      |
|                  | Leuprolide (Lupron Depot®, Eligard®) | Breast: 3.75 mg IM every 4 weeks<br>Prostate<br>• 7.5 mg SC or IM every 4 weeks<br>• 22.5 mg SC or IM every 12 weeks<br>• 30 mg SC or IM every 16 weeks<br>• 45 mg SC or IM every 24 weeks | HR-positive breast cancer<br>Prostate cancer | Injection site pain, mood changes, hot flashes, decreased libido, musculoskeletal weakness, decreased BMD, CVD (QTc prolongation, heart failure), gynecomastia (men)                                                                           | SC leuprolide (Eligard) is approved by the U.S. Food and Drug Administration for prostate cancer only. Temporary tumor flare (bladder outlet obstruction, bone pain, neurologic symptoms) may occur within the first few weeks after the initial dose secondary to initial increases in estradiol or testosterone level. Breast cancer must be HR-positive. (AbbVie, 2019)                                              |
|                  | Triptorelin (Trelstar®)              | 3.75 mg IM every 4 weeks<br>7.5 mg IM every 12 weeks<br>11.25 mg IM every 24 weeks                                                                                                         | Prostate cancer                              | Injection site pain, mood changes, hot flashes, decreased libido, musculoskeletal weakness, decreased BMD, CVD (QTc prolongation, heart failure), gynecomastia (men)                                                                           | Temporary tumor flare (bladder outlet obstruction, bone pain, neurologic symptoms) may occur within the first few weeks after the initial dose secondary to initial increases in estradiol or testosterone level. (Verity Pharmaceuticals, 2020)                                                                                                                                                                        |
| LHRH antagonists | Degarelix (Firmagon®)                | Loading: 240 mg SC once<br>Maintenance: 80 mg SC every 4 weeks                                                                                                                             | Prostate cancer                              | Injection site pain, mood changes, hot flashes, decreased libido, musculoskeletal weakness, decreased BMD, CVD (QTc prolongation, heart failure), gynecomastia (men)                                                                           | Administer immediately after reconstitution. Loading dose is administered as two 120 mg (3 ml) injections. Maintenance dose is administered as a single 4 ml injection. (Ferring Pharmaceuticals, 2020)                                                                                                                                                                                                                 |
|                  | Relugolix (Orgovyx™)                 | Loading: 360 mg PO once<br>Maintenance: 120 mg PO once daily                                                                                                                               | Prostate cancer                              | QT/QTc prolongation, embryo-fetal toxicity, hot flashes, hyperglycemia, hypertriglyceridemia, musculoskeletal pain, fatigue, anemia, increased liver enzymes (alanine aminotransferase and aspartate aminotransferase), constipation, diarrhea | Limit concurrent use with P-gp inhibitors and strong CYP3A inducers. If unavoidable, separate dosing 6 hours apart from a P-gp inhibitor and increase the dose to 240 mg PO if administered with a 3A4 or P-gp inducer. Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 2 weeks after the final dose of relugolix. (Myovant Sciences, 2020) |

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**TABLE 7-1.** Hormone Therapy Agents (*Continued*)

| Classification                         | Drug                               | Route and Dosing                                                                   | Indications                         | Side Effects                                                                                                                                                                                               | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                    |
|----------------------------------------|------------------------------------|------------------------------------------------------------------------------------|-------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Selective estrogen receptor modulators | Tamoxifen (Nolvadex <sup>®</sup> ) | Breast: 20 mg PO daily<br>Endometrial: 40 mg PO daily (one 20 mg dose twice daily) | Breast cancer<br>Endometrial cancer | Black box warnings: stroke, pulmonary embolism, uterine malignancies<br>Hyperlipidemia, BMD changes (increased in postmenopausal patients, decreased in premenopausal patients), hot flashes, mood changes | Certain selective serotonin reuptake inhibitors may reduce tamoxifen efficacy. Citalopram, escitalopram, and venlafaxine are preferred in place of other selective serotonin reuptake inhibitors. Another selective estrogen receptor modulator may be given if adverse effects are intolerable. Drug can be used in pre- or postmenopausal patients. (AstraZeneca Pharmaceuticals, 2021) |
|                                        | Raloxifene (Evista <sup>®</sup> )  | 60 mg PO daily                                                                     | Breast cancer risk reduction        | Black box warnings: stroke, deep vein thrombosis, pulmonary embolism<br>Hypertriglyceridemia, hot flashes, leg cramps                                                                                      | Use is not recommended in the following populations due to limited clinical efficacy and safety data: <ul style="list-style-type: none"> <li>• Premenopausal women</li> <li>• Men</li> <li>• Concomitant estrogen therapy</li> <li>• Renal and hepatic impairment</li> <li>• Prior history of breast cancer</li> </ul> (Eli Lilly and Company, 2022)                                      |

*Note.* Review package inserts for dosing and prescribing information.

BCRP—breast cancer resistance protein; BMD—bone mineral density; CVD—cardiovascular disease; CYP—cytochrome P450; GI—gastrointestinal; HR—hormone receptor; IM—intramuscular; LHRH—luteinizing hormone-releasing hormone; P-gp—P-glycoprotein; PO—by mouth; QTc—QT interval corrected; SC—subcutaneous; UGT—uridine diphosphate-glucuronosyltransferase



- (a) Upon reaching prostate tissue, testosterone and its precursors are transformed into the more potent androgen dihydrotestosterone.
    - (b) Androgens bind with and activate the androgen receptor, which results in physiologic effects.
    - (c) Androgens also serve as primary drivers in promoting prostate cancer growth and proliferation (NCCN, 2022; Zhou et al., 2018)
  - (3) Androgen deprivation therapy effectively slows the growth of prostate cancer cells.
    - (a) This can be accomplished by decreasing serum testosterone levels to castrate concentrations ( $< 50$  ng/dl) through orchiectomy or medication therapy (i.e., chemical castration).
    - (b) The expansion of oral and injectable pharmacologic agents in recent decades has led to a significant decline in the use of orchiectomy to treat prostate cancer (Crawford et al., 2019; NCCN, 2022).
  - (4) Over time, prostate cancers can become resistant to hormone therapy and lose androgen sensitivity, resulting in a resurgence in the growth and proliferation of prostate cancer cells and what is referred to as castration-resistant or hormone-refractory prostate cancer (Crawford et al., 2019).
- b) Breast cancer
- (1) Hormone receptor–positive breast cancer grows in response to action by estrogen or progesterone.
  - (2) Hormone receptor–positive breast cancer is the most common type and accounts for approximately 70% of all breast cancers (American Cancer Society, 2021).
  - (3) The ultimate goal of hormone therapy is to decrease concentrations of estrogens and progestins or prevent interaction with their receptors; however, treatment is highly dependent on whether a woman is premenopausal or postmenopausal and hormone receptor status (Burstein et al., 2018).
- c) Ovarian, endometrial, and uterine cancers
- (1) Endometrial carcinoma is the most common uterine cancer, followed by uterine sarcoma.
  - (2) First-line therapy consists of treatment with progestins. Second-line strategies include tamoxifen or tamoxifen in combination with progestins.
- (3) Of note, optimal responses are found most frequently in estrogen receptor (ER)–positive disease and endometrioid tumors (van Weelden et al., 2019).
- d) Adrenal cancer
- (1) Adrenocortical carcinomas are rare and occur mainly in adults.
  - (2) Although primary treatment is resection of the adrenal gland, adrenolytic antihormone therapy, with or without cytotoxic chemotherapy, is used for unresectable or widely metastatic tumors (National Cancer Institute, 2019).
- e) Thyroid cancers
- (1) Thyroidectomy followed by ablation with radioactive iodine is the usual treatment for most early-stage thyroid cancers.
    - (a) Radioactive iodine may be followed by the replacement of thyroid hormones (e.g., levothyroxine) in several clinical scenarios.
    - (b) Thyroglobulin and thyroid-stimulating hormone levels help evaluate response to therapy (Filetti et al., 2019).
  - (2) Hormone therapy is rarely used to treat metastatic or refractory disease (Filetti et al., 2019).
- f) Pituitary adenomas
- (1) Pituitary adenomas are classified as non-functioning, prolactin secreting (e.g., prolactinoma), growth hormone secreting (e.g., acromegaly), adrenocorticotrophic hormone secreting (e.g., Cushing disease), or thyrotropin secreting. Transsphenoidal surgical adenoma resection is the initial treatment chosen for all tumors except prolactinomas (Molitch, 2017).
  - (2) Dopamine agonists (e.g., bromocriptine, cabergoline) are used to achieve hormone control in patients with prolactinomas. Somatostatin analogs (e.g., octreotide, lanreotide) are used to manage acromegaly, Cushing disease, and thyrotropin-secreting tumors (Molitch, 2017).
- C. Hormone treatment categories
1. Luteinizing hormone–releasing hormone (LHRH) antagonists and agonists
    - a) LHRH antagonists and agonists are primarily used to treat breast and prostate cancer. Current literature demonstrates that concurrent radiation

therapy with LHRH antagonists and agonists in patients with prostate cancer improves overall survival in select nonmetastatic stages compared with standalone therapy (Crawford et al., 2019; Juloori et al., 2016).

- b) LHRH antagonists immediately block LHRH release from the hypothalamus, preventing the release of luteinizing hormone and follicle-stimulating hormone from the anterior pituitary gland (Crawford et al., 2019).
- c) LHRH agonists produce an initial increase in luteinizing hormone and follicle-stimulating hormone, which translates to increased testosterone concentrations (flare). Concentrations gradually reach castrate levels within two to four weeks, as LHRH release slows significantly in response to the downregulation of LHRH receptors in the anterior pituitary (Crawford et al., 2019).
- d) Although LHRH agonists and antagonists share similar side effect profiles, individuals receiving LHRH agonists may initially suffer from worsening symptoms at active cancer sites (e.g., urinary retention, bone pain) secondary to a phenomenon known as tumor flare.
  - (1) Symptoms of tumor flare will resolve as androgen levels decrease and can be prevented by adding a nonsteroidal antiandrogen during the first two weeks after LHRH agonist initiation.
  - (2) Other side effects of LHRH agonists include decreased bone mineral density, increased insulin resistance, dyslipidemia, increased visceral fat deposition, erectile dysfunction, decreased libido, neurocognitive changes, and depression (Crawford et al., 2019).
- e) LHRH agonists work similarly when used to treat breast cancer. These agents also downregulate the ovarian production of estrogen by preventing the release of luteinizing hormone. LHRH agonists are used in the adjuvant setting for women with ER-positive or progesterone receptor-positive premenopausal breast cancer with or without tamoxifen to reduce recurrence and preserve ovarian function (NCCN, 2021a).
- f) NCCN (2021a, 2022) guidelines for breast cancer recommend select LHRH agonists (e.g., leuprolide, goserelin) to treat breast cancer. The guidelines for prostate cancer state that LHRH antagonists (e.g., degarelix, relugolix) and agonists (e.g., leuprolide, goserelin, triptorelin) may be used interchangeably when androgen deprivation therapy is indicated.
- g) Nursing implications
  - (1) Recent literature has shown that men are particularly susceptible to specific car-

diovascular and metabolic adverse effects from LHRH agonist and antagonist therapy (Levine et al., 2010).

- (a) Nurses should educate men and their families on the increased risk for diabetes, heart attack, hypertension, weight gain, visceral fat deposition, loss of lean muscle mass, and bone fracture.
  - (b) Additionally, men can suffer from declines in psychosocial health, namely neurocognitive dysfunction and depression, which can sometimes be exacerbated by erectile dysfunction, hot flashes, and gynecomastia.
- (2) Counseling and social work services should be available to evaluate psychosocial health.
    - (a) Referral for medical services should be made for dyslipidemia or other cardiac issues, impaired glucose (e.g., abnormal blood glucose, increased hemoglobin A1c), and evaluation of bone mineral density, pain management, and nutrition as necessary.
    - (b) It is essential to include the patient's family and caregivers in the overall management plan.
  - (3) Women should be monitored for menopausal symptoms that may develop with endocrine therapy. Although estrogen supplementation is not recommended, nurses can assist women with other interventions to relieve symptoms. Metabolic syndrome and bone mineral density should also be regularly monitored.

## 2. Antiandrogens

- a) Antiandrogens block the effects of testosterone and dihydrotestosterone at their target receptors in tissues. As a result, they do not reduce the serum concentration of androgens and are not often used as single agents to treat prostate cancer (AA Pharma., 2019; ANI Pharmaceuticals, 2015; Astra-Zeneca Pharmaceuticals, 2017; NCCN, 2022).
- b) First-generation antiandrogens (e.g., bicalutamide, flutamide, nilutamide) are used in prostate cancer to mitigate tumor flare with LHRH agonists.
  - (1) They can also be adjunctive agents to LHRH agonist or antagonist therapy after disease progression in a treatment strategy known as combined androgen blockade.
  - (2) Although combined androgen blockade has been shown to achieve greater sup-

- pression of circulating testosterone and improve survival, it is associated with additional adverse events and poorer quality of life (Crawford et al., 2019).
- (3) Transaminitis and diarrhea are associated with the administration of first-generation agents. Nilutamide is also associated with visual field changes and disulfiram-like reactions.
  - (4) Because of disulfiram-like reactions, patients should be educated to avoid alcohol use while on therapy (AA Pharma., 2019; ANI Pharmaceuticals, 2015; AstraZeneca Pharmaceuticals, 2017).
  - c) Second-generation antiandrogens (e.g., enzalutamide, apalutamide, darolutamide) can be used as single agents or in combination with LHRH agonist or antagonist therapy (enzalutamide and apalutamide only) based on clinical features. These antiandrogens are primarily used in the castration-resistant prostate cancer setting (NCCN, 2022).
3. CYP17 inhibitors
    - a) Ketoconazole and abiraterone are indicated for prostate cancer treatment after progression on LHRH agonist or antagonist therapy (Janssen Pharmaceutical Companies, 2014, 2020b). Abiraterone is more widely used for castration-refractory prostate cancer (NCCN, 2022).
    - b) These agents decrease extragonadal production of androgens by inhibiting the CYP17 enzyme.
      - (1) This action blocks the formation of dehydroepiandrosterone from pregnenolone, thereby inhibiting the synthesis of androgens.
      - (2) Most extragonadal testosterone production occurs in the adrenal glands through steroid hormone biosynthesis pathways for which cholesterol is the precursor molecule (Janssen Pharmaceutical Companies, 2014, 2020b; Sewer & Li, 2008).
    - c) Ketoconazole and abiraterone are associated with transaminitis and mineralocorticoid excess.
      - (1) Symptoms of mineralocorticoid excess include hyperkalemia and fluid retention.
      - (2) These agents should not be used in patients with New York Heart Association class III or IV heart failure.
      - (3) To mitigate symptoms of mineralocorticoid excess and hypothalamus–pituitary–adrenal axis suppression, these agents should be given with low-dose oral corticosteroids (Janssen Pharmaceutical Companies, 2013, 2020b; NCCN, 2022).
  4. ER antagonists and selective ER downregulators
    - a) Fulvestrant is indicated for the treatment of metastatic ER-positive breast cancer alone or in combination with various agents (e.g., trastuzumab, CDK4/6 inhibitors, alpelisib) (AstraZeneca Pharmaceuticals, 2020; NCCN, 2021a).
    - b) Fulvestrant binds to an ER and degrades it. Both actions render circulating estrogen unable to exert its effects on breast cancer cells (AstraZeneca Pharmaceuticals, 2020).
    - c) Fulvestrant is relatively well tolerated and is occasionally associated with injection site pain and hot flashes (AstraZeneca Pharmaceuticals, 2020).
  5. Aromatase inhibitors (AIs)
    - a) These agents are also used to treat ER-positive breast cancer in premenopausal and postmenopausal women (NCCN, 2021a).
    - b) In premenopausal women, concomitant ovarian ablation with LHRH agonist therapy is recommended in the adjuvant, recurrent, or metastatic setting (NCCN, 2021a).
    - c) AIs are also used to treat ER-positive breast cancer in men. Therapy in men should be guided by treatment recommendations for AIs in postmenopausal women (NCCN, 2021a).
    - d) AIs are classified as steroidal (type 1) or nonsteroidal (type 2) and inhibit the conversion of aromatase, which converts androgens to estrogen.
      - (1) Steroidal AIs bind aromatase irreversibly.
      - (2) They inhibit aromatase by binding covalently to its receptor site. Nonsteroidal AIs (e.g., anastrozole, letrozole) bind reversibly.
      - (3) The blockade of aromatase is dependent on the continuous presence of the inhibitor, and aromatase will begin to release in its absence (Mantas et al., 2016).
    - e) Adverse effects of these agents include menopausal symptoms, decreased bone mineral density, and musculoskeletal disorders (Mantas et al., 2016).
  6. Selective estrogen receptor modulators (SERMs)
    - a) Raloxifene and tamoxifen are SERMs indicated for use in various breast cancer settings (AstraZeneca Pharmaceuticals, 2021; Eli Lilly and Company, 2022).
    - b) Although both can be used as preventive therapy for patients with high-risk invasive breast cancer, tamoxifen can also be used for patients with ductal carcinoma in situ, as adjuvant endocrine therapy, and for patients with hormone receptor-positive metastatic cancer (AstraZeneca Pharmaceuticals, 2021; Eli Lilly and Company, 2022; NCCN, 2021a).
    - c) Tamoxifen can also be used alone or in conjunction with progestins in certain populations

affected by endometrial cancer (NCCN, 2021b). SERMs are characterized by estrogenic and antiestrogen properties and can downregulate and block ERs in different tissues (Komm & Mirkin, 2014).

d) SERMs have been associated with an increased risk of deep vein thrombosis and pulmonary embolism (AstraZeneca Pharmaceuticals, 2021; Eli Lilly and Company, 2022). They have also been associated with the development of uterine malignancies, hyperlipidemia, and menopausal symptoms (AstraZeneca Pharmaceuticals, 2021; Komm & Mirkin, 2014).

e) The duration of therapy with SERMs in the adjuvant setting is highly dependent on menopausal status and whether a patient has been treated with an AI.

- (1) Generally, treatment lasts 5–10 years.
- (2) Patients can be transitioned to or from AI therapy within that time frame based on menopausal status and tolerance (Early Breast Cancer Trialists' Collaborative Group, 2015; Komm & Mirkin, 2014; Mirkin & Pickar, 2015; NCCN, 2021a).

f) Nursing implications

- (1) Blocking or eliminating estrogen will cause premature menopause in premenopausal women and heightened or renewed symptoms in perimenopausal and postmenopausal women.
- (2) SERMs may put women at higher risk for endometrial cancer and deep vein thrombosis. Adherence is challenging for patients on AIs and SERMs because of the discomfort of side effects, such as hot flashes, cognitive changes, fatigue, myalgias and arthralgias, and physical changes (Huober et al., 2014; Lombard et al., 2016).
- (3) Nurses can provide education and support to women undergoing this treatment. Additionally, some women benefit from participation in support groups with other women.

## 7. Adrenolytics

- a) Drug therapy with mitotane is indicated in unresectable or metastatic adrenocortical cancer or as adjuvant treatment following complete resection.
- b) Although its mechanism has not entirely been elucidated, mitotane acts within the adrenal cortex as a cytotoxic agent. As a result, it affects malignant and nonmalignant adrenocortical tissues.
- c) Mitotane is associated with nausea, vomiting, diarrhea, ataxia, amnesia, confusion, and suppression of hormones synthesized and released from the adrenal cortex (i.e., corticosteroids) (Corden Pharma Latina, 2021).

d) Nursing implications

- (1) Therapeutic and toxic effects are correlated with plasma concentration, requiring close monitoring and supportive management of adverse effects using hydrocortisone, antiemetics, and antidiarrheals.
- (2) Thyroid and androgen supplementation may also be necessary. Serum hormone concentrations should be assessed at least every three months in patients receiving mitotane.
- (3) Patients should be educated about adherence to mitotane therapy drug monitoring and other follow-up recommendations to limit the risk of drug discontinuation due to toxicity (Kerkhofs et al., 2015).

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## CHAPTER 8

# Targeted Therapy

### A. Targeted therapies in the treatment of cancer

1. Biomarker-directed antineoplastic agents selectively target molecular pathways that block the growth and spread of cancer, as opposed to traditional cytotoxic chemotherapy agents that target DNA, tubulin, or cell division machinery and are often less specific (National Cancer Institute, 2022).

- a) A growing number of unique molecular targets have been identified within cancer cells, resulting in the discovery of novel agents, many of which are administered via the oral route as tablets or capsules.
- b) The oral route allows for continuous administration of lower doses of agents, which may be primarily cytostatic, versus traditional infusional cytotoxic agents for which episodic delivery is necessary for adequate bone marrow recovery (National Cancer Institute, 2022).
- c) See Table 8-1 for a list of targeted therapies. Agents that target immune pathways and extracellular biomarkers are discussed in Chapter 10.
- d) Select targeted agents are designed to have activity against cancers with specific alterations or variants and may not have activity in cancers without the alteration. It is prudent to be aware of these specific indications when selecting therapy options for patients.

### 2. Tyrosine kinase inhibitors (TKIs)

- a) Tyrosine kinases direct many cellular functions, including cell signaling, growth, and division.
- b) These enzymes may be overly active in some cancer cells, and inhibition of them may stop cancer cell growth (National Cancer Institute, n.d.).
- c) See Figure 8-1 for a diagram of the basic principles of tyrosine kinases and Figure 8-2 for a depiction of epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) receptor pathways.
- d) When a TKI is introduced within these pathways, the enhanced activity is inhibited, leading

to decreased cell growth, proliferation, and differentiation (Zhong et al., 2021).

### 3. Agents by biomarker

#### a) Anaplastic lymphoma kinase (ALK) inhibitors

- (1) The fusion between echinoderm microtubule-associated protein-like 4 (EML4) and ALK is an oncogene present in 3%–5% of patients with non-small cell lung cancer, most commonly younger patients, never- or light-smokers with adenocarcinoma, and those without *EGFR* and *KRAS* driver variants (Khan et al., 2019).
- (2) The *ALK* gene rearrangement produces an abnormal ALK protein that leads to proliferation and survival of cancer cells through constitutive activation of RAS/RAF/MEK, PI3K/mTOR, and JAK/STAT pathways. (American Cancer Society, 2021).
- (3) Examples include alectinib (oral), brigatinib (oral), ceritinib (oral), crizotinib (oral), and lorlatinib (oral).

#### b) Breakpoint cluster region protein–Abelson tyrosine-protein kinase 1 (BCR-ABL1) TKIs

- (1) The BCR-ABL1 protein can become a driver variant resistant to some formulations of BCR-ABL1 TKIs.
- (2) Patients taking these medications for chronic myeloid leukemia require long-term therapy.
- (3) Data demonstrate the need for adherence monitoring, as adherent patients have a better early response and long-term outcomes (Cuellar et al., 2018).
- (4) Examples include imatinib (oral), bosutinib (oral), dasatinib (oral), nilotinib (oral), ponatinib (oral), and asciminib (oral).

#### c) *BRAF* V600E inhibitors and mitogen-activated extracellular signal regulated kinase (MEK) inhibitors



**TABLE 8-1.** Targeted Therapies

| Drug                       | Mechanism of Action                                                                                                                                    | Route | Indications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Side Effects                                                                                                                                                                                                                                                                  | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|----------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Abemaciclib (Verzenio®)    | Inhibits CDK4 and CDK6, which blocks cell cycle progression from G <sub>1</sub> into the S phase, resulting in cell senescence and apoptosis           | PO    | <p>HR-positive, HER2-negative advanced or metastatic breast cancer, in combination with fulvestrant, in patients with disease progression following endocrine therapy</p> <p>HR-positive, HER2-negative advanced or metastatic breast cancer, in combination with an aromatase inhibitor as initial endocrine-based therapy, in postmenopausal women</p> <p>HR-positive, HER2-negative advanced or metastatic breast cancer, as monotherapy, in patients with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting</p> <p>HR-positive, HER2-negative, and node-positive early breast cancer at high risk of recurrence and a Ki-67 score <math>\geq</math> 20%, as determined by an FDA-approved test, in combination with endocrine therapy (tamoxifen or an aromatase inhibitor) for adjuvant treatment, in adults</p> | <p>Common: diarrhea, neutropenia, nausea, abdominal pain, infections, fatigue, anemia, leukopenia, decreased appetite, vomiting, headache, thrombocytopenia, alopecia</p> <p>Severe: diarrhea, neutropenia, hepatotoxicity, venous thromboembolism, ILD/pneumonitis</p>       | <p>Patients should take twice daily, with or without food, at approximately the same time each day.</p> <p>The dose varies based on whether it is given in combination with endocrine therapy or as monotherapy.</p> <p>Tablets should not be crushed, chewed, or split.</p> <p>If patients vomit or miss a dose, they should take the next dose at its scheduled time.</p> <p>Tablets are supplied as 7-day dose packs.</p> <p>Avoid use in patients with severe hepatic impairment (Child-Pugh C).</p> <p>Drug interactions exist with CYP3A inhibitors (including grapefruit) and inducers.</p> <p>At the first sign of a loose stool, patients should start antidiarrheal therapy (e.g., loperamide), increase oral fluids, and notify their healthcare provider for further instructions. Diarrhea is most significant in the first month.</p> <p>Monitor CBC with differential and LFTs at baseline, every 2 weeks for 2 months, monthly for the next 2 months, then as clinically indicated.</p> <p>Women of reproductive potential should use contraception during treatment and for 3 weeks following completion of therapy. (Eli Lilly and Company, 2021a)</p> |
| Acalabrutinib (Calquence®) | Inhibits Bruton tyrosine kinase, which is a signaling molecule of the B-cell antigen receptor, leading to inhibition of malignant B-cell proliferation | PO    | <p>CLL or SLL</p> <p>Mantle cell lymphoma after at least 1 prior therapy</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | <p>Common: anemia, neutropenia, thrombocytopenia, upper respiratory tract infection, headache, diarrhea, musculoskeletal pain</p> <p>Severe: severe and opportunistic infections, second primary malignancies (skin cancers), atrial fibrillation and flutter, cytopenias</p> | <p>Patients should take every 12 hours, swallowing whole with water, with or without food. Capsules should not be chewed, broken, or opened.</p> <p>If patients miss a dose by more than 3 hours, they should skip it and take the next dose at its scheduled time.</p> <p>Avoid use in severe hepatic impairment.</p> <p>Drug interactions exist with strong and moderate CYP3A inhibitors (including grapefruit)</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

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**TABLE 8-1.** Targeted Therapies (*Continued*)

| Drug                                              | Mechanism of Action                                                                                                                              | Route | Indications                                                                                                                                                                               | Side Effects                                                                                                                                                                                                                              | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
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| Acalabrutinib<br>(Calquence®)<br>( <i>Cont.</i> ) |                                                                                                                                                  |       |                                                                                                                                                                                           |                                                                                                                                                                                                                                           | and strong inducers. Avoid coadministration with PPIs. Take acalabrutinib 2 hours before taking H <sub>2</sub> antagonists and separate dosing with antacids by at least 2 hours.<br>Monitor CBC with differential at regular intervals.<br>Advise patients to use sun protection.<br>Consider holding 3–7 days pre- and post-surgery depending on bleeding risk.<br>Women of reproductive potential should use contraception during treatment and for 1 week following completion of therapy.<br>(AstraZeneca Pharmaceuticals, 2019)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Afatinib<br>(Gilotrif®)                           | Binds to the tyrosine kinase domain of EGFR, HER2, and HER4; irreversibly inhibits autophosphorylation and down-regulation of signaling pathways | PO    | Metastatic NSCLC with EGFR exon 19 deletions or exon 21 (L858R) substitution variants, as first-line treatment<br>Metastatic squamous NSCLC progressing after platinum-based chemotherapy | Common: diarrhea, rash/acneiform dermatitis, stomatitis, paronychia, dry skin, decreased appetite, nausea, vomiting, pruritus<br>Severe: diarrhea, bullous and exfoliative skin disorders, ILD, hepatotoxicity, GI perforation, keratitis | Patients should take once daily at least 1 hour before or 2 hours after a meal.<br>If patients miss a dose by more than 12 hours, they should skip it and take the next dose at its scheduled time.<br>Drug interactions exist with P-gp inhibitors and inducers, requiring dose modification.<br>Dose modifications are recommended in severe renal impairment (glomerular filtration rate 15–29 mL/min/1.73 m <sup>2</sup> ).<br>LFTs should be monitored periodically.<br>Diarrhea may be severe enough to lead to dehydration and renal failure. Patients should take an antidiarrheal agent (e.g., loperamide) at the onset of diarrhea until loose bowel movements cease for 12 hours.<br>Contact lens use increases the risk of keratitis and ulceration.<br>Advise patients to minimize sun exposure and use broad-spectrum sunscreen.<br>Women of reproductive potential should use contraception during treatment and for 2 weeks following completion of therapy.<br>(Boehringer Ingelheim Pharmaceuticals, 2019) |

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**TABLE 8-1.** Targeted Therapies (Continued)

| Drug                  | Mechanism of Action                                                                                                                           | Route | Indications                                                                                                                                                                                                      | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                                    | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
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| Alectinib (Alecensa®) | TKI that targets ALK and RET to decrease tumor cell viability in cell lines harboring ALK fusions, amplifications, or activating variants     | PO    | ALK-positive metastatic NSCLC                                                                                                                                                                                    | Common: fatigue, constipation, edema, myalgia, anemia<br>Severe: hepatotoxicity, ILD, bradycardia, CPK elevation, renal impairment, hemolytic anemia                                                                                                                                                                                                                                                                            | <p>Patients should take every 12 hours with food. Do not open or dissolve the contents of the capsule.</p> <p>If patients miss or vomit a dose, they should take the next dose at the scheduled time. Dose modifications are recommended for severe hepatic impairment (Child-Pugh C). Monitor heart rate and BP regularly. Monitor LFTs every 2 weeks for 3 months, then once monthly and as clinically indicated. Monitor CPK levels every 2 weeks for 1 month and as clinically indicated. Advise patients to report any unexplained muscle pain, tenderness, or weakness. The median time to grade 3 CPK elevation is 14 days.</p> <p>Advise patients to minimize sun exposure and use broad-spectrum sunscreen during treatment and for at least 7 days after discontinuation.</p> <p>Women of reproductive potential should use contraception during treatment and for 1 week following completion of therapy. Males with female partners of reproductive potential should use contraception during treatment and for 3 months following completion of therapy. (Genentech, 2021)</p> |
| Apelisib (Piqray®)    | Inhibits PI3K, with inhibitory activity predominantly against PI3K- $\alpha$ ; inhibits the PI3K/AKT signaling pathway to reduce tumor growth | PO    | HR-positive, HER2-negative, PI3KCA-variated, advanced or metastatic breast cancer in men and postmenopausal women, in combination with fulvestrant, following progression on or after an endocrine-based regimen | Common: increased glucose, increased creatinine, diarrhea, rash, decreased lymphocyte count, increased gamma glutamyl transferase, nausea, increased ALT, increased lipase, fatigue, decreased hemoglobin, decreased appetite, stomatitis, vomiting, weight loss, decreased calcium, decreased glucose, prolonged activated partial thromboplastin time, alopecia<br>Severe: hypersensitivity, cutaneous reactions, pneumonitis | <p>Patients should take once daily with food. Tablets should not be crushed, chewed, or split prior to swallowing.</p> <p>If patients miss a dose, it can be taken within 9 hours after the time it is usually taken. After more than 9 hours, patients should skip the dose for that day.</p> <p>If patients vomit a dose, they should skip that dose and take the usual dose the following day.</p> <p>Before initiating treatment, test fasting plasma glucose and hemoglobin A1c; optimize blood glucose. After initiating treatment, monitor blood glucose once weekly for 2 weeks, then at least once every 4 weeks and</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

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**TABLE 8-1.** Targeted Therapies (*Continued*)

| Drug                                      | Mechanism of Action                                                                                                                                                                                              | Route | Indications                                                                                                                                   | Side Effects                                                                                                                                                                                                                                                                                                                                                                               | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
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| Alpelisib<br>(Piqray)<br>( <i>Cont.</i> ) |                                                                                                                                                                                                                  |       |                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                            | <p>as clinically indicated. Monitor hemoglobin A1c every 3 months and as clinically indicated. Initiate or optimize antihyperglycemic medications as clinically indicated.</p> <p>Advise patients to start antidiarrheal treatment, increase oral fluids, and notify their healthcare provider if diarrhea occurs. Interrupt, reduce dose, or discontinue if severe diarrhea occurs.</p> <p>Drug interactions exist with CYP3A4 inducers, BCRP inhibitors, and CYP2C9 substrates. Women of reproductive potential and males with female partners of reproductive potential should use contraception during treatment and for 1 week following completion of therapy.</p> <p>(Novartis Pharmaceuticals, 2019)</p>                                                                                                                                                                                                                                                                                                                                   |
| Asciminib<br>(Scemblix <sup>®</sup> )     | Inhibits ABL1 kinase activity of the BCR-ABL1 fusion protein by binding to the ABL myristoyl pocket; has activity against wild-type BCR-ABL1 and several variant forms of the kinase, including T315I alteration | PO    | <p>Ph-positive CML in chronic phase, previously treated with 2 or more TKIs</p> <p>Ph-positive CML in chronic phase with T315I alteration</p> | <p>Common: upper respiratory tract infections, musculoskeletal pain, fatigue, nausea, rash, diarrhea, decreased platelets, increased triglycerides, decreased ANC, decreased hemoglobin, increased creatinine kinase, increased ALT, increased lipase, increased amylase</p> <p>Severe: myelosuppression, pancreatic toxicity, hypertension, hypersensitivity, cardiovascular toxicity</p> | <p>Patients should take once daily or twice daily depending on dose and indication. The drug should be taken on an empty stomach. Patients should avoid food for at least 2 hours before or 1 hour after taking the drug. Tablets should be swallowed whole. Tablets should not be broken, crushed, or chewed. Once-daily dosing regimen: If patients miss a dose by more than 12 hours, they should skip the dose and take the next dose as scheduled.</p> <p>Twice-daily dosing regimen: If patients miss a dose by more than 6 hours, they should skip the dose and take the next dose as scheduled.</p> <p>Drug interactions exist with strong CYP3A4 inhibitors, itraconazole oral solutions containing hydroxypropyl-beta-cyclodextrin, certain substrates of CYP3A4, substrates of CYP2C9, and certain P-gp substrates. Monitor CBCs every 2 weeks for the first 3 months of treatment, then monthly thereafter. Monitor serum lipase and amylase monthly. Perform more frequent monitoring in patients with a history of pancreatitis.</p> |

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**TABLE 8-1.** Targeted Therapies (*Continued*)

| Drug                                                | Mechanism of Action                                                                                                                                                                                              | Route     | Indications                                                                                                                                             | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|-----------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|---------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>Asciminib<br/>(Scemblix®)<br/>(<i>Cont.</i>)</p> |                                                                                                                                                                                                                  |           |                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | <p>Monitor BP.</p> <p>Monitor for signs and symptoms of hypersensitivity.</p> <p>Monitor patients with a history of cardiovascular risk factors for cardiovascular signs and symptoms.</p> <p>Women of reproductive potential should use contraception during treatment and for 1 week following completion of therapy.</p> <p>(Novartis Pharmaceuticals, 2021e)</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <p>Avapritinib<br/>(Ayvakit™)</p>                   | <p>Targets PDGFR-alpha, PDGFR-alpha D842V, KIT D816V, and KIT exon variants, inhibiting autophosphorylation and constitutive action of these receptors and possibly contributing to tumor cell proliferation</p> | <p>PO</p> | <p>Unresectable or metastatic GIST with a PDGFR-alpha exon 18 variant, including PDGFR-alpha D842V alteration</p> <p>Advanced systemic mastocytosis</p> | <p>Common: edema, nausea, fatigue/asthenia, cognitive impairment, vomiting, diarrhea, decreased appetite, abdominal pain, increased eye tearing, constipation, rash, hair color changes, dizziness, intracranial bleeding, severe headache, vision problems, severe sleepiness, severe weakness on one side of body</p> <p>Severe: CNS effects, including forgetfulness, confusion, getting lost, trouble thinking, drowsiness, dizziness, trouble sleeping, word-finding problems, hallucinations, changes in mood or behavior</p> | <p>Patients should take once daily on an empty stomach at least 1 hour before and 2 hours after a meal.</p> <p>Instruct patients that if they miss a dose, it should not be taken within 8 hours of the next scheduled dose. Patients should not take an additional dose if vomiting occurs.</p> <p>Drug interactions exist with CYP3A inhibitors and inducers.</p> <p>Monitor patients for signs of intracranial hemorrhage and CNS side effects, including cognitive impairment, dizziness, sleep disorders, speech and mood disorders, and hallucinations. Median time to onset of first CNS adverse reaction is 6.1 weeks.</p> <p>Women of reproductive potential and males with female partners of reproductive potential should use effective contraception during treatment and for 6 weeks following completion of therapy.</p> <p>(Blueprint Medicines, 2021a)</p> |

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**TABLE 8-1.** Targeted Therapies (*Continued*)

| Drug                               | Mechanism of Action                                                                                                                               | Route | Indications                                                                                                                                                                                                                 | Side Effects                                                                                                                                                                                                                                                                                                                                   | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
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| Axitinib<br>(Inlyta <sup>®</sup> ) | Inhibits tyrosine kinases, including VEGFR1, VEGFR2, and VEGFR3, leading to interferences with tumor angiogenesis, growth, and cancer progression | PO    | Advanced RCC, in combination with avelumab as first-line treatment<br>Advanced RCC, in combination with pembrolizumab as first-line treatment<br>Advanced RCC, as a single agent, after failure of 1 prior systemic therapy | Common: hypertension, diarrhea, fatigue/asthenia, palmar-plantar erythrodysesthesia (hand-foot syndrome), nausea, decreased appetite, musculoskeletal pain, mucositis, hypothyroidism, hepatotoxicity, rash, abdominal pain, headache, dysphonia, cough, decreased weight, vomiting, constipation<br>Severe: hypertension, hypertensive crisis | <p>Patients should take every 12 hours, swallowing whole with a glass of water, with or without food.</p> <p>If patients vomit or miss a dose, they should not take an additional dose. Advise patients to take the next prescribed dose at the regularly scheduled time.</p> <p>Dose modifications are recommended for moderate hepatic impairment (Child-Pugh B). No data are available for severe hepatic impairment (Child-Pugh C).</p> <p>Drug interactions exist with CYP3A4/5 inhibitors, (including grapefruit) and inducers.</p> <p>Dosing should be held beginning at least 48 hours before elective surgery because of the risk of impaired wound healing. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. Time to restart therapy is based on clinical judgment.</p> <p>Do not use in patients with untreated brain metastasis or recent active GI bleeding because of risk of hemorrhage.</p> <p>BP should be well-controlled prior to initiating the drug. Monitor for hypertension and treat as needed.</p> <p>Monitor thyroid function, urine for proteinuria, ALT, AST, and bilirubin before initiation and periodically throughout treatment.</p> <p>Monitor for arterial and venous thromboembolic events.</p> <p>Consider more frequent monitoring of ALT, AST, and bilirubin for patients receiving the drug in combination with avelumab or pembrolizumab.</p> <p>Women of reproductive potential and males with female partners of reproductive potential should use effective contraception during treatment and for 1 week following completion of therapy.</p> <p>(Pfizer, 2020b)</p> |

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**TABLE 8-1.** Targeted Therapies (Continued)

| Drug                                | Mechanism of Action                                                                                                                                                                                                   | Route | Indications                                       | Side Effects                                                                                                                                                                                                                                                                 | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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| Belinostat (Beleodaq <sup>®</sup> ) | Inhibits HDAC, causing accumulation of acetylated histones and other proteins, leading to cell cycle arrest or apoptosis of transformed cells; preferential cytotoxicity toward tumor cells compared to healthy cells | IV    | Relapsed or refractory peripheral T-cell lymphoma | <p>Common: anemia, hepatotoxicity, nausea, fatigue, fever, vomiting, diarrhea, constipation, dyspnea, rash, peripheral edema</p> <p>Severe: hematologic toxicity (e.g., thrombocytopenia, leukopenia, anemia), infections (e.g., pneumonia, sepsis), hepatotoxicity, TLS</p> | <p>Infuse IV on days 1–5 of a 21-day cycle. Administer over 30 minutes with a 0.22-micron in-line filter. If infusion pain or other symptoms potentially attributable to the infusion occur, infusion time may be extended to 45 minutes.</p> <p>The infusion bag with drug solution may be stored at room temperature for up to 36 hours, including infusion time.</p> <p>Drug interactions exist with strong inhibitors of UGT1A1.</p> <p>Avoid use in patients with moderate or severe hepatic dysfunction and severe renal dysfunction.</p> <p>ANC should be <math>\geq 1,000/\text{mm}^3</math> and platelet count should be <math>\geq 50,000/\text{mm}^3</math> prior to the start of each cycle.</p> <p>Monitor CBC with differential at baseline and weekly.</p> <p>Monitor serum chemistry tests (including renal and liver function) prior to the start of each cycle.</p> <p>Monitor patients with advanced stage disease and high tumor burden for TLS.</p> <p>Women of reproductive potential should use effective contraception during treatment and for 6 months following completion of therapy. Males with female partners of reproductive potential should use effective contraception during treatment and for 3 months following completion of therapy.</p> <p>Drug is cytotoxic. Follow hazardous drug handling and disposal procedures. (Acrotech Biopharma, 2020)</p> |

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**TABLE 8-1.** Targeted Therapies (*Continued*)

| Drug                                | Mechanism of Action                                                                                                                                                                                                                                     | Route | Indications                                                                                                    | Side Effects                                                                                                                                                                                                                                                                                                               | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
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| Binimetinib (Mektovi <sup>®</sup> ) | Inhibits MEK1 and MEK2 activity, which inhibits ERK phosphorylation; in combination with encorafenib, targets two different kinases in the RAS/RAF/MEK/ERK pathway, resulting in greater antiproliferative activity in BRAF variant-positive cell lines | PO    | Unresectable or metastatic melanoma with a <i>BRAF</i> V600E or V600K variant, in combination with encorafenib | Common: fatigue, nausea and vomiting, diarrhea, abdominal pain, visual disturbances, increased creatinine, increased CPK, increased LFTs<br>Severe: cardiomyopathy; venous thromboembolism; ocular toxicities, including retinopathy, retinal vein occlusion, and uveitis; ILD; hepatotoxicity; rhabdomyolysis; hemorrhage | <p>Patients should take twice daily (every 12 hours), with or without food.</p> <p>If patients miss a dose, they should skip the missed dose if within 6 hours of the next scheduled dose.</p> <p>If patients vomit a dose, an additional dose should not be taken. Advise patients to take the next prescribed dose at the usual time.</p> <p>Dose modification is recommended for patients with moderate or severe hepatic impairment.</p> <p>Assess LVEF before initiating treatment, after one month of treatment, then every 2–3 months thereafter.</p> <p>Perform an ophthalmologic evaluation at regular intervals and for any visual disturbances.</p> <p>Monitor LFTs before and monthly during treatment and as clinically indicated.</p> <p>Monitor CPK and creatinine periodically and as clinically indicated.</p> <p>If encorafenib is permanently discontinued, then discontinue binimetinib.</p> <p>The drug may interact with radiation and lead to increased CNS, pulmonary, dermatologic, and visceral toxicity. Consider holding <math>\geq 3</math> days before and after fractionated radiation and <math>\geq 1</math> day before and after stereotactic radiosurgery.</p> <p>Women of reproductive potential should use effective contraception during treatment and for 30 days after completion of therapy. (Array BioPharma, 2020b; National Comprehensive Cancer Network, 2022)</p> |

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**TABLE 8-1.** Targeted Therapies (Continued)

| Drug                  | Mechanism of Action                                                                                                                                                       | Route  | Indications                              | Side Effects                                                                                                                                                                                                                                                                                                                                                                        | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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| Bortezomib (Velcade®) | Inhibits chymotrypsin-like activity of 26S proteasome, resulting in disruption of proteolysis, which is needed for cellular homeostasis, ultimately leading to cell death | IV, SC | Multiple myeloma<br>Mantle cell lymphoma | <p>Common: peripheral neuropathy, neuralgia, nausea, vomiting, diarrhea, constipation, fatigue, thrombocytopenia, neutropenia, anemia, leukopenia, lymphopenia, rash, fever, anorexia</p> <p>Severe: peripheral neuropathy, hypotension, cardiac failure, pulmonary toxicity, RPLS, GI toxicity, thrombocytopenia, neutropenia, TLS, hepatotoxicity, thrombotic microangiopathy</p> | <p>Inject SC or IV once or twice weekly, depending on the specific regimen.</p> <p>For SC injection, the administration site should be rotated in the thigh or abdomen. Select new site at least 1 inch from previous site and avoid tender or bruised areas. Consider use of a less concentrated SC injection (1 mg/ml) for patients that experience local injection site reactions.</p> <p>For IV administration, administer as a 3- to 5-second bolus.</p> <p>The drug is given via routes other than SC or IV.</p> <p>Reconstitute only with NS. Use reconstituted solution within 8 hours. Concentrations of SC (2.5 mg/ml) and IV (1 mg/ml) doses are different, and final volume depends on calculated dose.</p> <p>Dose modification is recommended for patients with moderate or severe hepatic impairment.</p> <p>Drug interactions exist with strong CYP3A4 inhibitors (including grapefruit) and strong inducers. Patients on an oral antidiabetic agent require close monitoring of their blood glucose and may need adjustment of their antidiabetic medication.</p> <p>Monitor CBC frequently during treatment. Platelet count is recommended prior to each dose.</p> <p>There is less peripheral neuropathy with the SC route compared to the IV route.</p> <p>Women of reproductive potential should use effective contraception during treatment and for 7 months after completion of therapy. Males with female partners of reproductive potential should use effective contraception during treatment and for 4 months after completion of therapy.</p> <p>Follow hazardous drug handling and disposal procedures.</p> <p>(Millennium Pharmaceuticals, 2019)</p> |

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**TABLE 8-1.** Targeted Therapies (*Continued*)

| Drug                      | Mechanism of Action                                                                                                                                                                                                                          | Route | Indications                                                                                                                                      | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|---------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|--------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Bosutinib<br>(Bosulif®)   | Inhibits BCR-ABL1 tyrosine kinase created by the Ph-positive genetic abnormality, inhibiting proliferation, and induces apoptosis in BCR-ABL1-positive cell lines; also inhibits Src family kinases (Src, Lyn, Hck)                          | PO    | Newly diagnosed chronic phase Ph-positive CML<br>Chronic, accelerated, or blast phase Ph-positive CML resistant or intolerant to other therapies | Common: diarrhea, rash, nausea, vomiting, abdominal pain, fatigue, hepatic dysfunction, respiratory tract infection, fever, headache, thrombocytopenia, anemia, neutropenia, increased creatinine, decreased calcium, increased CPK, increased amylase, increased lipase<br>Severe: fluid retention presenting as pericardial effusion, pulmonary edema, peripheral edema, GI toxicity, myelosuppression, hepatic toxicity, cardiovascular toxicity, renal toxicity | Patients should take daily with food. Dose varies based on indication. Tablets should not be crushed or cut. If patients miss a dose beyond 12 hours, they should skip the dose and take the usual dose on the following day. Concomitant use with CYP3A4 inhibitors (including grapefruit) or inducers may alter exposure to the drug. Use of PPIs may reduce drug concentration and is not recommended. Use of antacids or H <sub>2</sub> antagonists should be separated from bosutinib administration by more than 2 hours. Monitor renal function at baseline and during therapy. Monitor liver enzymes at least monthly for the first 3 months and as needed. Hold dosing and adjust dose if severe or persistent thrombocytopenia or neutropenia occurs. Hold dosing if other clinically significant moderate or severe nonhematologic toxicities occur, then restart once symptoms abate. (Pfizer, 2021a) |
| Brigatinib<br>(Alunbrig®) | Multikinase inhibitor that targets ALK, insulin-like growth factor 1 receptor, FLT3, ROS1, and EGFR, which inhibits subsequent downstream signaling proteins signal transducer and activator of transcription 3 (STAT3), Akt, ERK1/2, and S6 | PO    | ALK-positive metastatic NSCLC                                                                                                                    | Common: diarrhea, fatigue, nausea, rash, cough, myalgia, headache, hypertension, vomiting, dyspnea<br>Severe: ILD/pneumonitis, hypertension, bradycardia, visual disturbance, CPK elevation, pancreatic enzyme elevation, hyperglycemia                                                                                                                                                                                                                             | Patients should take once daily with or without food. Tablets should be taken whole and not crushed or chewed. Dose should be increased on day 7 if tolerated. If drug therapy is interrupted for 14 days or longer, resume treatment at lower starting dose. If patients miss or vomit a dose, they should skip the dose and take the usual dose the following day. Dose modification is recommended for severe hepatic impairment (Child-Pugh C) and severe renal impairment (CrCl 15–29 ml/min). Drug interactions exist with moderate and strong CYP3A inhibitors (including grapefruit) and moderate and strong CYP3A inducers.                                                                                                                                                                                                                                                                              |

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**TABLE 8-1.** Targeted Therapies (Continued)

| Drug                                                         | Mechanism of Action                                                                                                                                                                                                                                | Route | Indications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|--------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Brigatinib<br>(Alunbrig®)<br>(Cont.)                         |                                                                                                                                                                                                                                                    |       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Optimize BP prior to initiation. Monitor BP after 2 weeks and at least monthly during treatment. Monitor heart rate regularly. Monitor CPK, amylase, and lipase levels regularly during treatment. Monitor serum glucose at baseline and regularly during treatment. Women of reproductive potential should use contraception during treatment and for 4 months following completion of therapy. Males with female partners of reproductive potential should use contraception during treatment and for 3 months following completion of therapy. Hormonal contraceptives may be ineffective because of decreased exposure when used concurrently with brigatinib. (Takeda Pharmaceuticals, 2020)                                                                                                                                                        |
| Cabozantinib<br>(Cometriq® [capsules]; Cabometyx® [tablets]) | Inhibits tyrosine kinase activity of multiple receptor kinases (including RET, MET, VEGFR, KIT, TRKB, FLT3, ROS1, AXL, TYRO3, MER, TIE-2) involved with oncogenesis, metastasis, tumor angiogenesis, and maintenance of the tumor microenvironment | PO    | Cometriq capsules: progressive, metastatic, medullary thyroid cancer<br>Cabometyx tablets <ul style="list-style-type: none"> <li>• Advanced RCC</li> <li>• Advanced RCC, in combination with nivolumab as first-line treatment</li> <li>• HCC previously treated with sorafenib</li> <li>• Locally advanced or metastatic differentiated thyroid cancer that has progressed following prior VEGFR-targeted therapy in adult and pediatric patients ≥ 12 years of age who are refractory to or ineligible for radioactive iodine</li> </ul> | Common: diarrhea, stomatitis, palmar-plantar erythrodysesthesia, decreased weight, decreased appetite, nausea, fatigue, oral pain, hair color changes, dysgeusia, hypertension, abdominal pain, constipation, increased AST/ALT, lymphopenia, increased ALP, hypocalcemia, neutropenia, thrombocytopenia, hypophosphatemia, hyperbilirubinemia<br>Severe: perforations and fistulas, hemorrhage, thrombotic events (e.g., myocardial infarction, cerebral infarction), impaired wound healing, hypertension, osteonecrosis of the jaw, diarrhea, palmar-plantar erythrodysesthesia, proteinuria, RPLS | Do not substitute Cometriq capsules for Cabometyx tablets or vice versa. Patients should take once daily without food. Patients should not eat at least 2 hours before and 1 hour after taking cabozantinib. Capsules should be swallowed whole and not opened. Missed doses should not be taken within 12 hours of the next dose. Dose adjustments are required in patients with mild to moderate hepatic impairment (Child-Pugh A and B). Drug interactions exist with strong CYP3A4 inhibitors (including grapefruit) and strong CYP3A4 inducers. Hold drug for at least 3 weeks prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. Hold for at least 3 weeks prior to invasive dental procedure and for development of osteonecrosis of the jaw. Monitor urine for protein. |

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**TABLE 8-1.** Targeted Therapies (Continued)

| Drug                                                                    | Mechanism of Action                                                                                        | Route | Indications                                                                                          | Side Effects                                                                                                                                  | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
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| Cabozantinib<br>(Cometriq® [capsules]; Cabometyx® [tablets])<br>(Cont.) |                                                                                                            |       |                                                                                                      |                                                                                                                                               | Monitor BP regularly. Interrupt for hypertension not adequately controlled with antihypertensive therapy.<br>Women of reproductive potential should use contraception during treatment and for 4 months following completion of therapy.<br>Capsules are dispensed as blister cards. (Exelixis, 2020, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Capmatinib<br>(Tabrecta™)                                               | Kinase inhibitor that targets MET, which inhibits proliferation and survival of MET-dependent cancer cells | PO    | Metastatic NSCLC with an alteration that leads to mesenchymal epithelial transition exon 14 skipping | Common: peripheral edema, nausea, vomiting, fatigue, dyspnea, decreased appetite<br>Severe: ILD/pneumonitis, hepatotoxicity, photosensitivity | Patients should take every 12 hours, with or without food, at the same time each day. Tablets should not be broken, crushed, or chewed.<br>Instruct patients to discard any unused drug remaining after 6 weeks of first opening the bottle.<br>If patients miss or vomit a dose, they should skip the dose and take the next dose at the regularly scheduled time.<br>Advise patients to limit direct ultraviolet light exposure, use sunscreen, and wear protective clothing.<br>Monitor LFTs prior to the start of treatment, every 2 weeks for the first 3 months, then once a month or as clinically indicated.<br>Many drug interactions exist, including strong CYP3A inhibitors (including grapefruit), moderate and strong CYP3A inducers, CYP1A2 substrates, P-gp and BCRP substrates, and MATE1 and MATE2 substrates.<br>Women of reproductive potential and males with female partners of reproductive potential should use contraception during treatment and for 1 week following the completion of therapy.<br>(Novartis Pharmaceuticals, 2020c) |

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**TABLE 8-1.** Targeted Therapies (Continued)

| Drug                    | Mechanism of Action                                                                                  | Route | Indications                                                                                                                                                                                                                                                                                                                                                                                                                            | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
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| Carfilzomib (Kyprolis®) | Binds to and inhibits the 20S proteasome, resulting in antiproliferative and proapoptotic activities | IV    | <p>Relapsed or refractory multiple myeloma in patients who have received 1–3 lines of therapy in combination with the following:</p> <ul style="list-style-type: none"> <li>• Lenalidomide and dexamethasone</li> <li>• Dexamethasone</li> <li>• Daratumumab (IV or SC) and dexamethasone</li> </ul> <p>Relapsed or refractory multiple myeloma, as a single agent, in patients who have received at least 1 prior line of therapy</p> | <p>Common: anemia, fatigue, thrombocytopenia, nausea, fever, dyspnea, diarrhea, headache, cough, peripheral edema, hypertension</p> <p>Severe: cardiac failure or ischemia, acute renal failure, TLS, pulmonary toxicity (acute respiratory distress syndrome, acute respiratory failure, acute diffuse infiltrative pulmonary disease), pulmonary hypertension, dyspnea, hypertension including hypertensive crisis, venous thromboembolism, infusion reactions, hemorrhage, thrombocytopenia, anemia, hepatotoxicity and hepatic failure, thrombotic microangiopathy, posterior reversible encephalopathy, progressive multifocal leukoencephalopathy</p> | <p>Administer IV over 10 or 30 minutes depending on the regimen. If patient's BSA exceeds 2.2 m<sup>2</sup>, calculate the dose based on a BSA of 2.2 m<sup>2</sup>.</p> <p>Adequate hydration is recommended prior to cycle 1, especially in patients at high-risk for TLS or renal toxicity. Recommended hydration includes oral fluids (30 ml/kg at least 48 hours before cycle 1, day 1) and IV fluids (250–500 ml of appropriate fluid). Consider posthydration with IV fluids.</p> <p>Premedicate with dexamethasone PO/IV prior to each dose during the first cycle and in subsequent cycles if infusion reactions occur. Premedication should be given at least 30 minutes, but no more than 4 hours, prior to all doses.</p> <p>Dose modification is recommended for mild or moderate hepatic impairment.</p> <p>For patients on hemodialysis, administer after dialysis procedure.</p> <p>Monitor serum potassium, renal function, LFTs, and CBC regularly during treatment. Optimize BP prior to treatment. Monitor BP regularly while on treatment.</p> <p>Antiviral prophylaxis should be considered to decrease risk of herpes zoster reactivation. Thromboprophylaxis should be administered in patients receiving concurrent therapy with dexamethasone or lenalidomide.</p> <p>Women of reproductive potential should use contraception during treatment and for 6 months following the completion of therapy. Males with female partners of reproductive potential should use contraception during treatment and for 3 months following final dose.</p> <p>Drug is cytotoxic. Follow hazardous drug handling and disposal procedures. (Onyx Pharmaceuticals, 2021)</p> |

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**TABLE 8-1.** Targeted Therapies (*Continued*)

| Drug                              | Mechanism of Action                                                                                                                                              | Route | Indications                    | Side Effects                                                                                                                                                                                                                                 | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
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| Ceritinib (Zykadia <sup>®</sup> ) | Kinase inhibitor that targets ALK, insulin-like growth factor 1 receptor, insulin receptor, and ROS1, which inhibits proliferation of ALK-dependent cancer cells | PO    | ALK-positive, metastatic NSCLC | <p>Common: diarrhea, nausea, vomiting, abdominal pain, fatigue, decreased appetite, weight loss</p> <p>Severe: GI adverse reactions, hepatotoxicity, ILD/pneumonitis, QT interval prolongation, hyperglycemia, bradycardia, pancreatitis</p> | <p>Patients should take once daily with food. The drug is available as a tablet or capsule. If patients miss a dose, they should take that dose unless the next dose is due within 12 hours. If vomiting occurs, patients should not take an additional dose and continue with the next scheduled dose.</p> <p>Dose modifications are recommended for severe hepatic impairment (Child-Pugh C). Drug interactions exist with CYP3A4 inhibitors (including grapefruit), CYP3A inducers, CYP3A4 substrates, CYP2C9 substrates (e.g., fentanyl, warfarin), other drugs that prolong QTc interval, and drugs that cause bradycardia.</p> <p>Monitor heart rate and BP regularly. Advise patients to report any changes in heart or BP medication.</p> <p>Monitor LFTs at least monthly</p> <p>Monitor lipase, amylase, and fasting glucose prior to treatment and periodically during treatment.</p> <p>Monitor ECG and electrolytes for patients with CHF, bradyarrhythmias, electrolyte abnormalities, or those taking other medications that prolong QTc interval.</p> <p>Women of reproductive potential should use contraception during treatment and for 6 months following completion of therapy. Males with female partners of reproductive potential should use contraception during treatment and for 3 months following completion of therapy.</p> <p>(Novartis Pharmaceuticals, 2021g)</p> |

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**TABLE 8-1.** Targeted Therapies (Continued)

| Drug                                 | Mechanism of Action                                                                                                                                                                                                                             | Route | Indications                                                                                                     | Side Effects                                                                                                                                                                                                                                                                                                                                                                    | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
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| Cobimetinib (Cotellic <sup>®</sup> ) | Reversible inhibitor of MAPK/MEK1 and MEK2, leading to inhibition of tumor cell growth                                                                                                                                                          | PO    | Unresectable or metastatic melanoma with <i>BRAF</i> V600E or V600K alteration, in combination with vemurafenib | <p>Common: diarrhea, photosensitivity, nausea, vomiting, fever, increased gamma glutamyl transferase, increased CPK, hypophosphatemia, increased LFTs, lymphopenia, hyponatremia</p> <p>Severe: second primary malignancies (cutaneous and non-cutaneous), hemorrhage, cardiomyopathy, severe skin rash, retinopathy/retinal vein occlusion, hepatotoxicity, rhabdomyolysis</p> | <p>Patients should take once daily, with or without food, for the first 21 days of a 28-day cycle.</p> <p>If patients miss or vomit a dose, they should skip the dose and take the usual dose on the following day.</p> <p>Drug interactions exist with moderate and strong CYP3A4 inhibitors (including grapefruit) and CYP3A4 inducers.</p> <p>Evaluate LVEF before treatment, after 1 month of treatment, then every 3 months during treatment.</p> <p>Monitor patients for second malignancies prior to initiation of therapy, while on therapy, and for up to 6 months following the completion of therapy.</p> <p>Perform an ophthalmologic evaluation at regular intervals and for any visual disturbances.</p> <p>Monitor LFTs prior to initiation, monthly during treatment, and as clinically indicated.</p> <p>Monitor CPK prior to initiation and periodically during treatment.</p> <p>Advise patients to minimize sun exposure and use broad-spectrum sunscreen and lip balm (SPF <math>\geq</math> 30).</p> <p>Women of reproductive potential should use contraception during treatment and for 2 weeks following completion of therapy. (Genentech, 2018)</p> |
| Copanlisib (Aliqopa <sup>®</sup> )   | Inhibits PI3K with inhibitory activity predominantly against PI3K-alpha and PI3K-delta isoforms expressed in malignant B cells, leading to induction of tumor cell death by apoptosis and inhibition of proliferation of malignant B-cell lines | IV    | Relapsed follicular lymphoma in patients who have received at least 2 prior systemic therapies                  | <p>Common: hyperglycemia, hypertension, diarrhea, decreased general strength and energy, leukopenia, neutropenia, thrombocytopenia, nausea, lower respiratory tract infections</p> <p>Severe: infections, noninfectious pneumonitis, hyperglycemia, hypertension, neutropenia, severe cutaneous reactions</p>                                                                   | <p>Administer IV over 60 minutes on days 1, 8, and 15 of a 28-day treatment cycle.</p> <p>Dilute reconstituted solution in 100 ml NS.</p> <p>Dose modifications are recommended for patients with moderate hepatic impairment (Child-Pugh B).</p> <p>Concomitant use with CYP3A4 inhibitors (including grapefruit) or CYP3A4 inducers may alter exposure to copanlisib.</p> <p>Consider PJP prophylaxis for populations at risk.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

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**TABLE 8-1.** Targeted Therapies (*Continued*)

| Drug                                         | Mechanism of Action                                                                                                                                      | Route | Indications                                                                                                                                             | Side Effects                                                                                                                                                                                                                                                                              | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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| Copanlisib<br>(Aliqopa®)<br>( <i>Cont.</i> ) |                                                                                                                                                          |       |                                                                                                                                                         |                                                                                                                                                                                                                                                                                           | <p>Blood glucose levels typically peak 5–8 hours following infusion and subsequently decline to baseline in most patients. Optimize blood glucose control before starting each infusion.</p> <p>Monitor BP preinfusion and postinfusion. BP typically remains elevated for 6–8 hours following infusion. Withhold treatment until both systolic BP is &lt; 150 mm Hg and diastolic BP is &lt; 90 mm Hg.</p> <p>Monitor CBC at least weekly during treatment. Women of reproductive potential and males with female partners of reproductive potential should use contraception during treatment and for 1 month after completion of therapy.</p> <p>(Bayer HealthCare Pharmaceuticals, 2021a)</p>                                                                                                                                                                                                                     |
| Crizotinib<br>(Xalkori®)                     | Inhibits multiple tyrosine kinases, including ALK, hepatocyte growth factor receptor, ROS1, and RON, which reduces tumor cell proliferation and survival | PO    | Metastatic ALK-positive or ROS1-positive NSCLC<br>Relapsed or refractory, ALK-positive ALCL in pediatric patients aged 1 year or older and young adults | <p>Common: vision disorders, nausea, vomiting, diarrhea, edema, constipation, elevated transaminases, fatigue, decreased appetite, upper respiratory tract infection, dizziness, neuropathy</p> <p>Severe: hepatotoxicity, ILD/pneumonitis, QT prolongation, bradycardia, vision loss</p> | <p>Patients should take twice daily with or without food.</p> <p>Dosing is BSA based for lymphoma indication. Capsules should not be crushed, chewed, or opened.</p> <p>If patients miss a dose, they should take that dose unless the next dose is within 6 hours. If vomiting occurs after taking a dose, patients should take the next dose at the regularly scheduled time.</p> <p>Antiemetics are recommended prior to and during treatment if used to treat ALCL.</p> <p>Dose modifications are recommended for patients with moderate and severe hepatic impairment and severe renal impairment (CrCl &lt; 30 ml/min).</p> <p>Drug interactions exist with CYP3A inhibitors (including grapefruit), CYP3A inducers, and CYP3A4 substrates (e.g., fentanyl, midazolam).</p> <p>Monitor CBC with differential monthly and as clinically indicated; monitor weekly for the first month if used to treat ALCL.</p> |

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**TABLE 8-1.** Targeted Therapies (Continued)

| Drug                                | Mechanism of Action                                                                                                                                                                                             | Route | Indications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|-------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Crizotinib<br>(Xalkori®)<br>(Cont.) |                                                                                                                                                                                                                 |       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                               | <p>Monitor LFTs every 2 weeks for the first 2 months of treatment, then monthly and as clinically indicated.</p> <p>Monitor ECG and electrolytes in patients with CHF bradyarrhythmias, electrolyte abnormalities (e.g., hypomagnesemia, hypokalemia), and those taking medications that prolong QT interval.</p> <p>Monitor heart rate and BP regularly. Advise patients to report any changes in heart or BP medications.</p> <p>If treating ALCL, obtain baseline ophthalmologic examination prior to starting treatment, within 1 month of starting therapy, every 3 months thereafter, and upon any new visual symptoms. If treating NSCLC, obtain ophthalmologic examination for any new onset visual symptoms.</p> <p>Women of reproductive potential should use contraception during treatment and for 45 days following completion of therapy. Males with female partners of reproductive potential should use condoms during treatment and for 90 days following completion of therapy.<br/>(Pfizer, 2021c)</p> |
| Dabrafenib<br>(Tafinlar®)           | Inhibits some altered forms of BRAF kinases to inhibit tumor cell growth. Dabrafenib and trametinib target two different kinases in the RAS/RAF/MEK/ERK pathway, leading to greater inhibition of tumor growth. | PO    | <p>Unresectable or metastatic melanoma with <i>BRAF</i> V600E alteration, as a single agent</p> <p>In combination with trametinib for the following:</p> <ul style="list-style-type: none"> <li>• Unresectable or metastatic melanoma with <i>BRAF</i> V600E or V600K alteration</li> <li>• Adjuvant treatment of melanoma with <i>BRAF</i> V600E or V600K alterations and involvement of lymph node(s) following complete resection</li> <li>• NSCLC with <i>BRAF</i> V600E variation</li> </ul> | <p>Common: hyperkeratosis, headache, fever, arthralgia, papuloma, alopecia, palmar-plantar erythrodysesthesia, rash (in combination with trametinib), diarrhea (in combination with trametinib)</p> <p>Severe: second primary malignancies (cutaneous and non-cutaneous), tumor promotion in BRAF wild-type melanoma, hemorrhage, cardiomyopathy, uveitis, febrile reactions, serious to mild skin rash, hyperglycemia, hemolytic anemia, hyperkeratosis,</p> | <p>Patients should take twice daily approximately 12 hours apart and at least 1 hour before or 2 hours after a meal.</p> <p>Capsules should not be opened, crushed, or broken.</p> <p>Patients should not take a missed dose within 6 hours of the next dose.</p> <p>Drug interactions exist with CYP3A4 or CYP2C8 inhibitors (including grapefruit) and substrates of CYP3A4 (i.e., midazolam), CYP2C8, CYP2C9, (i.e., warfarin), CYP2C19, and CYP2B6. Hormone contraceptives may be ineffective because of decreased exposure when used concurrently with dabrafenib. Monitor INR levels more frequently in patients receiving warfarin.</p>                                                                                                                                                                                                                                                                                                                                                                            |

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| TABLE 8-1. Targeted Therapies (Continued) |                     |       |                                                                                                                                                                                                     |                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|-------------------------------------------|---------------------|-------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Drug                                      | Mechanism of Action | Route | Indications                                                                                                                                                                                         | Side Effects                                                                                                                                             | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Dabrafenib<br>(Tafinlar®)<br>(Cont.)      |                     |       | <ul style="list-style-type: none"><li>Locally advanced or meta-static anaplastic thyroid cancer with <i>BRAF</i> V600E alteration and with no satisfactory locoregional treatment options</li></ul> | headache, arthralgia, papil-loma, alopecia, hand-foot syn-drome, cough, fatigue, nausea, vomiting, diarrhea, dry skin, anorexia, edema, chills, dys-pnea | <p>Assess LVEF before initiation, 1 month after initiation, and then at intervals of 2–3 months while on treatment.</p> <p>Withhold for fever of <math>\geq 101.3^{\circ}\text{F}</math> or fever complicated by hypotension, rigors/chills, dehydration, or renal failure. For patients who develop a severe febrile reaction or fever associated with complications, administer antipyretics as secondary prophylaxis when resuming dabrafenib. Administer corticoste-roids (prednisone 10 mg daily) for at least 5 days for second or subsequent develop-ment of fever if temperature does not return to baseline within 3 days of onset.</p> <p>Perform dermatologic evaluations prior to ini-tiation, every 2 months while on therapy, and up to 6 months after discontinuation.</p> <p>Monitor for signs or symptoms of noncutane-ous malignancies.</p> <p>Monitor serum glucose levels in patients with preexisting diabetes or hyperglycemia.</p> <p>Women of reproductive potential should use nonhormonal contraception during treat-ment and for at least 2 weeks following com-pletion of therapy. Men with female partners of reproductive potential should use effec-tive contraception during treatment and for at least 2 weeks after completion of therapy.</p> <p>The drug may interact with radiation and lead to increased CNS, pulmonary, dermatologic, and visceral toxicity. Consider holding <math>\geq 3</math> days before and after fractionated radia-tion and <math>\geq 1</math> day before and after stereotac-tic radiosurgery.</p> <p>(National Comprehensive Cancer Network, 2022; Novartis Pharmaceuticals, 2021f)</p> |

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**TABLE 8-1.** Targeted Therapies (Continued)

| Drug                    | Mechanism of Action                                                                                                                                                                                    | Route | Indications                                                                                                                                                                                                                                                                                                                                                                                                                       | Side Effects                                                                                                                                                                                                                                                                                                                                               | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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| Dacomitinib (Vizimpro®) | Irreversible inhibitor of the kinase activity of the human EGFR family (EGFR/HER1, HER2, HER4) and certain EGFR-activating alterations (exon 19 deletion or the exon 21 L858R substitution alteration) | PO    | Metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution alteration, as first-line treatment                                                                                                                                                                                                                                                                                                                     | Common: diarrhea, rash, paronychia, stomatitis, decreased appetite, dry skin, decreased weight, alopecia, cough, pruritus<br>Severe: ILD, diarrhea, dermatologic adverse reactions                                                                                                                                                                         | Patients should take once daily at the same time each day, with or without food.<br>If patients vomit or miss a dose, they should skip the dose and take the usual dose the following day.<br>Drug interactions exist with CYP2D6 substrates and PPIs. Avoid the use of PPIs with dacomitinib. Administer dacomitinib at least 6 hours before or 10 hours after an H <sub>2</sub> antagonist.<br>Promptly initiate antidiarrheal treatment (loperamide or diphenoxylate hydrochloride with atropine sulfate) for diarrhea.<br>Most patients develop a rash. Incidence and severity of rash may increase with sun exposure. Advise patients to use moisturizers and to minimize sun exposure with protective clothing and sunscreen at the time of initiation.<br>Women of reproductive potential should use effective contraception during treatment and for 17 days following completion of therapy. (Pfizer, 2020e) |
| Dasatinib (Sprycel®)    | Inhibits multiple tyrosine kinases, including BCR-ABL, Src family, KIT, ephrin type-A receptor 2, and PDGFR-beta                                                                                       | PO    | Ph-positive CML in chronic phase, as first-line treatment<br>Chronic, accelerated, or myeloid or lymphoid blast phase<br>Ph-positive CML with resistance or intolerance to prior therapy, including imatinib<br>Ph-positive ALL with resistance or intolerance to prior therapy<br>Ph-positive CML in chronic phase or newly diagnosed<br>Ph-positive ALL in pediatric patients ≥ 1 year of age, in combination with chemotherapy | Common: myelosuppression, fluid retention (e.g., pleural effusions), diarrhea, headache, rash, hemorrhage, dyspnea, fatigue, nausea, musculoskeletal pain<br>Severe: myelosuppression, bleeding events, fluid retention (including pleural effusions), cardiac dysfunction, pulmonary arterial hypertension, QT prolongation, dermatologic toxicities, TLS | Patients should take once daily, with or without food, either in the morning or in the evening.<br>Tablets should not be crushed, cut, or chewed.<br>Drug interactions exist with CYP3A4 inhibitors (including grapefruit) and CYP3A4 inducers. Use of PPIs or H <sub>2</sub> antagonists may reduce drug concentration and is not recommended. Use of antacids should be separated from administration of dasatinib by ≥ 2 hours.<br>Monitor CBC every 2 weeks for 3 months, then every 3 months or as clinically indicated for patients with chronic phase CML and weekly for 2 months and monthly thereafter for patients with advanced phase CML or ALL.<br>Correct hypokalemia and hypomagnesemia prior to and during treatment to minimize risk of QTc prolongation.                                                                                                                                            |

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**TABLE 8-1.** Targeted Therapies (*Continued*)

| Drug                                        | Mechanism of Action                                                                                                                                    | Route | Indications                                                                                                                                                | Side Effects                                                                                                                                                                                                                                                                                       | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
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| Dasatinib<br>(Sprycel®)<br>( <i>Cont.</i> ) |                                                                                                                                                        |       |                                                                                                                                                            |                                                                                                                                                                                                                                                                                                    | Fluid retention is typically managed by diuretics or short courses of steroids. Severe pleural effusion may require thoracentesis and oxygen therapy.<br>Women of reproductive potential and males with female partners of reproductive potential should use effective contraception during treatment and for 30 days following completion of therapy.<br>(Bristol-Myers Squibb, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Duvelisib<br>(Copiktra®)                    | Kinase inhibitor of PI3K, with inhibitory activity predominantly against PI3K-delta and PI3K-gamma isoforms expressed in healthy and malignant B cells | PO    | Relapsed or refractory CLL or SLL after at least 2 prior therapies<br>Relapsed or refractory follicular lymphoma after at least 2 prior systemic therapies | Common: neutropenia, diarrhea/colitis, rash, fatigue, fever, cough, nausea, upper respiratory infection, pneumonia, musculoskeletal pain, anemia<br>Black box warnings: infections, diarrhea/colitis, cutaneous reactions, pneumonitis<br>Other severe adverse events: hepatotoxicity, neutropenia | Patients should take twice daily, 12 hours apart, at the same time each day, with or without food.<br>Capsules should be swallowed whole. They should not be opened, broken, or chewed.<br>If patients miss a dose, it can be taken within 6 hours of the missed time. If a dose is missed by > 6 hours, patients should skip the dose and take the usual dose the following day.<br>Drug interactions exist with CYP3A inducers, CYP3A inhibitors (including grapefruit), and CYP3A substrates.<br>Monitor ANC at least every 2 weeks for the first 2 months of therapy.<br>Monitor liver function during treatment.<br>Provide prophylaxis for PJP during treatment. Following completion of treatment, continue prophylaxis until absolute CD4-positive T-cell count > 200/mm <sup>3</sup> .<br>Monitor for signs and symptoms of infection. The most common serious infections were pneumonia, sepsis, and lower respiratory infections.<br>The median time to onset of any grade diarrhea or colitis was 4 months.<br>Women of reproductive potential and males with female partners of reproductive potential should use effective contraception for 1 month following the completion of therapy.<br>(Verastem, 2019) |

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**TABLE 8-1.** Targeted Therapies (Continued)

| Drug                    | Mechanism of Action                                                                                                                                                                                          | Route | Indications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Side Effects                                                                                                                                                                                                                                                                                                                                                                                             | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
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| Eltrombopag (Promacta®) | TPO receptor agonist that interacts with the transmembrane domain of the human TPO receptor and initiates signaling cascades that induce proliferation and differentiation from bone marrow progenitor cells | PO    | Thrombocytopenia in adult and pediatric patients (≥ 1 year old) with chronic immune thrombocytopenia who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy<br>Thrombocytopenia with chronic hepatitis C to allow initiation and maintenance of interferon-based therapy<br>Severe aplastic anemia in adult and pediatric patients ≥ 2 years of age, in combination with standard immunosuppressive therapy as first-line treatment<br>Severe aplastic anemia with an insufficient response to immunosuppressive therapy | Common: anemia, nausea, pyrexia, increased ALT, cough, fatigue, headache, diarrhea<br>Black box warnings: In patients with chronic hepatitis C, eltrombopag in combination with interferon and ribavirin may increase the risk of hepatic decompensation.<br>Other severe adverse events: hepatotoxicity, increased risk of death and progression of MDS to AML, thrombotic/thromboembolic complications | The drug is available as tablets and an oral suspension.<br>Patients should take once daily without a meal or with a meal low in calcium (≤ 50 mg). Patients should take at least 2 hours before or 4 hours after other medications (e.g., antacids), calcium-rich foods, or supplements containing polyvalent cations (e.g., iron, calcium aluminum, magnesium, selenium, zinc). Patients should not split, chew, or crush tablets and mix with food or liquids.<br>Prior to using the oral suspension, patients or caregivers must receive proper education on dosing, preparation, and administration. Administer the oral suspension immediately after preparation. Discard any suspension not administered within 30 minutes of preparation. Prepare with water only. Do not use hot water.<br>Dose modifications are recommended for patients with mild, moderate, or severe hepatic impairment and some patients of East Asian ancestry.<br>Adjust dose to maintain a platelet count ≥ 50,000/mm <sup>3</sup> . Do not exceed 75 mg daily.<br>Monitor CBC with differential weekly until a stable platelet count has been achieved, then monitor monthly thereafter.<br>Monitor LFTs prior to initiation, every 2 weeks during dose adjustment phase, and monthly with stable dose.<br>Perform a baseline ocular examination prior to initiation and during therapy. Monitor for signs and symptoms of cataracts.<br>If no hematologic response has occurred after 16 weeks of therapy, discontinue the drug.<br>(Novartis Pharmaceuticals, 2021c) |

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**TABLE 8-1.** Targeted Therapies (*Continued*)

| Drug                    | Mechanism of Action                                                                                               | Route | Indications                                        | Side Effects                                                                                                                                                                                                                                                                                                                                                            | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
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| Enasidenib<br>(Idhifa®) | Inhibits the IDH2 enzyme, leading to decreased 2-hydroxyglutarate levels and induction of myeloid differentiation | PO    | Relapsed or refractory AML with an IDH2 alteration | <p>Common: nausea, vomiting, diarrhea, elevated bilirubin, decreased appetite</p> <p>Black box warning: differentiation syndrome (symptoms: fever, dyspnea, acute respiratory distress, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, lymphadenopathy, bone pain, and hepatic, renal, and multiorgan dysfunction)</p> | <p>Patients should take once daily, at approximately the same time each day with or without food.</p> <p>For patients without disease progression or unacceptable toxicity, treat for a minimum of 6 months to allow time for response.</p> <p>Patients should not split or crush tablets; instruct patients to swallow whole with a cup of water.</p> <p>If a dose is vomited, missed, or not taken at the usual time, administer the dose as soon as possible on the same day, and return to the normal schedule the following day.</p> <p>Patients should not take 2 doses to make up for the missed dose.</p> <p>If differentiation syndrome is suspected, initiate PO or IV corticosteroids (e.g., dexamethasone 10 mg every 12 hours). Taper only after resolution of symptoms.</p> <p>Drug interactions exist with OATP1B1, OATP1B3, BCRP, and P-gp substrates.</p> <p>Monitor CBC and blood chemistries prior to initiation and at least every 2 weeks for the first 3 months of treatment.</p> <p>Hormonal contraceptives may be ineffective because of decreased exposure when used concurrently with enasidenib. Women of reproductive potential and men with female partners of reproductive potential should use contraception during treatment and for 2 months following completion of therapy.</p> <p>(Celgene, 2021a)</p> |

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**TABLE 8-1.** Targeted Therapies (Continued)

| Drug                                 | Mechanism of Action                                    | Route | Indications                                                                                                                                                                                                                                                                    | Side Effects                                                                                                                                                                             | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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| Encorafenib (Braftovi <sup>®</sup> ) | Targets <i>BRAF</i> V600E to inhibit tumor cell growth | PO    | Unresectable or metastatic melanoma with a <i>BRAF</i> V600E or V600K alteration, in combination with binimetinib<br>Metastatic colorectal cancer with a <i>BRAF</i> V600E alteration, as detected by an FDA-approved test, in combination with cetuximab, after prior therapy | Common: fatigue, nausea, vomiting, abdominal pain, arthralgia<br>Severe: hemorrhage, uveitis, QT prolongation, new primary malignancies, tumor promotion in <i>BRAF</i> wild-type tumors | <p>Patients should take once daily with or without food.</p> <p>Patients should not take a missed dose if within 12 hours of the next scheduled dose. Patients should not take an additional dose if vomiting occurs but continue with the next scheduled dose.</p> <p>Drug interactions exist with CYP3A4 inhibitors (including grapefruit), CYP3A4 inducers, and CYP3A4 substrates. Avoid coadministration with hormonal contraceptives.</p> <p>Perform dermatologic evaluations prior to therapy, every 2 months while on therapy, and for up to 6 months following discontinuation.</p> <p>Monitor patients for signs and symptoms of noncutaneous malignancies.</p> <p>Perform ophthalmologic evaluation at regular intervals and for any visual disturbances.</p> <p>Monitor electrolytes before and during treatment. Monitor ECG for patients who already have or who are at significant risk for developing QTc prolongation (e.g., known long QT syndromes, clinically significant bradyarrhythmias).</p> <p>Women of reproductive potential and men with female partners of reproductive potential should use contraception during treatment and for 2 weeks following completion of therapy. Advise females to use an effective nonhormonal contraception because encorafenib can decrease effectiveness.</p> <p>The drug may interact with radiation and lead to increased CNS, pulmonary, dermatologic, and visceral toxicity. Consider holding <math>\geq 3</math> days before and after fractionated radiation and <math>\geq 1</math> day before and after stereotactic radiosurgery.</p> <p>(Array BioPharma, 2020a; National Comprehensive Cancer Network, 2022)</p> |

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**TABLE 8-1.** Targeted Therapies (*Continued*)

| Drug                        | Mechanism of Action                                                                                          | Route | Indications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                         | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
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| Entrectinib<br>(Rozlytrek™) | Kinase inhibitor of TRK (encoded by <i>NTRK</i> genes), proto-oncogene tyrosine-protein kinase ROS1, and ALK | PO    | <p>Metastatic ROS1-positive NSCLC in adult patients</p> <p>Adult and pediatric patients aged <math>\geq 12</math> years with solid tumors with the following characteristics:</p> <ul style="list-style-type: none"> <li>• <i>NTRK</i> gene fusion without a known acquired resistance alteration</li> <li>• Metastatic disease or if surgical resection is likely to result in severe morbidity</li> <li>• Progression following treatment or no satisfactory alternative treatment</li> </ul> | <p>Common: fatigue, constipation, dysgeusia, edema, dizziness, diarrhea, nausea, dysesthesia, dyspnea, myalgia, cognitive impairment, increased weight, cough, vomiting, pyrexia, arthralgia, vision disorders</p> <p>Severe: CHF, CNS effects (e.g., cognitive impairment, mood disorders, dizziness, sleep disturbances), skeletal fractures, hepatotoxicity, hyperuricemia, QT prolongation, vision disorders</p> | <p>Patients should take once daily with or without food.</p> <p>Capsules should be swallowed whole. They should not be opened, crushed, chewed, or dissolved.</p> <p>If patients miss a dose, it can be taken unless the next dose is due within 12 hours.</p> <p>If patients vomit immediately after taking a dose, they should repeat that dose.</p> <p>Drug interactions exist with moderate and strong CYP3A inhibitors (including grapefruit), and moderate and strong CYP3A inducers.</p> <p>Assess LVEF prior to initiation in patients with symptoms or known risk factors for CHF.</p> <p>Monitor patients for clinical signs of CHF.</p> <p>Monitor QT interval and electrolytes at baseline and periodically during treatment for patients who already have or who are at significant risk of developing QTc prolongation.</p> <p>Assess serum uric acid levels prior to initiation and periodically during treatment. Monitor for signs and symptoms of hyperuricemia.</p> <p>Monitor for CNS effects, including seizures, hallucinations, and changes in cognitive function, mood (including suicidal ideation), speech, mental status, and sleep.</p> <p>Monitor LFTs every 2 weeks for the first month of treatment then monthly thereafter.</p> <p>Women of reproductive potential should use effective contraception during treatment and for 5 weeks following completion of therapy. Males with female partners of reproductive potential should use effective contraception during treatment and for 3 months following completion of therapy. (Genentech, 2019)</p> |

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**TABLE 8-1.** Targeted Therapies (Continued)

| Drug                              | Mechanism of Action                                                                                                                                                                                                                              | Route     | Indications                                                                                                                                                                                                                                                                                                                   | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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| <p>Erdaftinib<br/>(Balversa™)</p> | <p>Kinase inhibitor that binds to and inhibits enzymatic activity of FGFR1, FGFR2, FGFR3, and FGFR4; also binds to RET, CSF1R, PDGFR-alpha, PDGFR-beta, FLT4, KIT, and VEGFR2; demonstrates antitumor activity in FGFR-expressing cell lines</p> | <p>PO</p> | <p>Locally advanced or metastatic urothelial carcinoma with susceptible <i>FGFR3</i> or <i>FGFR2</i> genetic alterations that has progressed during or following at least a single line of prior platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy</p> | <p>Common: hyperphosphatemia, stomatitis, fatigue, anemia, increased SCr, diarrhea, dry mouth, onycholysis, elevated LFTs, hyponatremia, decreased appetite, hypoalbuminemia, dysgeusia, decreased hemoglobin, dry skin, dry eyes, alopecia, hypomagnesemia, constipation, palmar-plantar erythrodysesthesia, hypercalcemia, abdominal pain, nausea, musculoskeletal pain<br/>Severe: retinopathy/retinal pigment epithelial detachment, hyperphosphatemia</p> | <p>Patients should take once daily, with or without food, at approximately the same time each day.<br/>Dose may be increased 2–3 weeks after initiation based on serum phosphate levels and tolerability.<br/>Tablets should not be crushed, chewed, or split. If patients miss a dose, they should take it as soon as possible on the same day. Resume the regular daily dose schedule the next day. If patients vomit a dose, they should take the next dose on the next day.<br/>Drug interactions exist with moderate and strong CYP2C9 and CYP3A4 inhibitors (including grapefruit), moderate and strong CYP2C9 and CYP3A4 inducers, serum phosphate level-altering agents, CYP3A4 substrates, OCT2 substrates, and P-gp substrates.<br/>Monitor for CNS effects, including seizures, hallucinations, changes in cognitive function, mood (including suicidal ideation), speech, mental status, and sleep.<br/>Perform monthly ophthalmologic examinations during the first 4 months of treatment, every 3 months thereafter, and for any visual symptoms.<br/>All patients should receive dry eye prophylaxis with ocular demulcents as needed. Assess serum phosphate levels 14–21 days after initiation, then monthly during treatment.<br/>Women of reproductive potential and males with female partners of reproductive potential should use effective nonhormonal birth control during treatment and for 1 month following completion of therapy.<br/>(Janssen Biotech, 2020)</p> |

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**TABLE 8-1.** Targeted Therapies (*Continued*)

| Drug                                                                     | Mechanism of Action                                                                                                                                             | Route | Indications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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| Erlotinib<br>(Tarceva®)                                                  | Inhibits the kinase activity of EGFR, preventing autophosphorylation of tyrosine residues associated with EGFR, inhibiting further downstream signaling         | PO    | Metastatic NSCLC that has EGFR exon 19 deletions or exon 21 (L858R) substitution alterations, for first-line, maintenance, or second or subsequent treatment following at least 1 prior chemotherapy regimen<br>Locally advanced, unresectable, or metastatic pancreatic cancer, as first-line treatment in combination with gemcitabine                                                                                                                                                                                                                                          | Common: rash, diarrhea, anorexia, fatigue, dyspnea, cough, nausea, vomiting<br>Severe: ILD (e.g., dyspnea, cough, fever), renal failure, hepatotoxicity, GI perforations, bullous and exfoliative skin disorders, cerebrovascular accident (with pancreatic cancer), microangiopathic hemolytic anemia (with pancreatic cancer), ocular disorders, hemorrhage in combination with warfarin                                                                              | Patients should take once daily on an empty stomach at least 1 hour before or 2 hours after food.<br>Drug interactions exist with CYP3A4 and CYP1A2 inhibitors (including grapefruit). Cigarette smoking may decrease erlotinib concentrations; avoid concomitant use.<br>Drugs that increase gastric pH decrease erlotinib concentrations. Avoid concomitant use of PPIs. For H <sub>2</sub> antagonists, take erlotinib 10 hours after H <sub>2</sub> antagonist. For antacids, separate dosing by several hours.<br>Monitor renal function, electrolytes, and LFTs periodically during treatment.<br>Regularly monitor INR in patients receiving warfarin. Monitor for GI bleeding and elevated INR.<br>Diarrhea can be managed using loperamide.<br>Women of reproductive potential should use contraception during treatment and for at least 1 month following completion of therapy. (Genentech, 2016) |
| Everolimus<br>(Afinitor®, Afinitor Disperz® tablets for oral suspension) | Inhibits mTOR, which is a serine-threonine kinase downstream of the PI3K/Akt pathway, resulting in reduced cell proliferation, angiogenesis, and glucose uptake | PO    | Advanced HR-positive, HER2-negative breast cancer in postmenopausal women, in combination with exemestane after failed treatment with letrozole or anastrozole<br>Postmenopausal women with advanced HR-positive, HER2-negative breast cancer in combination with exemestane after failed treatment with letrozole or anastrozole<br>Progressive NET of pancreatic origin and progressive, well-differentiated, nonfunctional NETs of lung or GI origin that are unresectable, locally advanced, or metastatic<br>Advanced RCC after failed treatment with sunitinib or sorafenib | Common: stomatitis, infections, rash, fatigue, diarrhea, edema, abdominal pain, nausea, fever, asthenia, cough, headache, decreased appetite<br>Severe: noninfectious pneumonitis, infections, angioedema, hypersensitivity reactions, stomatitis, renal failure, impaired wound healing, myelosuppression, metabolic disorders (e.g., hyperglycemia, hyperlipidemia), risk of infection or reduced immune response with vaccination, radiation sensitization or recall | Patients should take once daily, with or without food, at the same time each day.<br>Tablets should not be broken or crushed.<br>If patients miss a dose, they can take it up to 6 hours after the time it is normally taken.<br>Double doses should not be taken to make up a missed dose.<br>Pediatric dose is based on BSA.<br>Disperz tablets can be used to prepare an oral suspension in an oral syringe or small drinking glass. See prescribing information for detailed preparation instructions.<br>Dose modification may be recommended for patients with hepatic impairment (Child-Pugh A, B, and C).<br>Drug interactions exist with CYP3A4 and P-gp inhibitors (including grapefruit) or CYP3A4 and P-gp inducers.<br>Patients should avoid live vaccines and close contact with those who have received live vaccines.                                                                         |

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**TABLE 8-1.** Targeted Therapies (Continued)

| Drug                                                                                | Mechanism of Action | Route | Indications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Side Effects | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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| Everolimus<br>(Afinitor®, Afinitor Disperz® tablets for oral suspension)<br>(Cont.) |                     |       | <p>Renal angiomyolipoma and tuberous sclerosis complex not requiring immediate surgery</p> <p>Tuberous sclerosis complex in patients who have subependymal giant cell astrocytoma that requires therapeutic intervention but cannot be resected</p> <p><i>Note.</i> Afinitor is not indicated for the treatment of patients with functional carcinoid tumors.</p> <p>Afinitor and Afinitor Disperz are indicated for the treatment of adult and pediatric patients aged ≥ 1 year with tuberous sclerosis complex who have subependymal giant cell astrocytoma that requires therapeutic intervention but cannot be curatively resected.</p> <p>Afinitor Disperz is indicated for the adjunctive treatment of adult patients and pediatric patients aged ≥ 2 years with partial-onset seizures associated with tuberous sclerosis complex.</p> |              | <p>Stomatitis most often occurs within the first 8 weeks of treatment. Initiating dexamethasone alcohol-free mouthwash as a swish and spit reduces the incidence and severity of stomatitis. Patients should avoid alcohol-, hydrogen peroxide-, iodine-, or thyme-containing products, as they may exacerbate the condition.</p> <p>Monitor renal function, lipid panel, and fasting serum glucose prior to initiation of therapy and at least annually thereafter. Monitor fasting serum glucose more frequently in patients with diabetes.</p> <p>Monitor CBC prior to initiation, every 6 months for the first year, and annually thereafter.</p> <p>Hold drug for at least 1 week prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing.</p> <p>Patients taking concomitant angiotensin-converting enzyme inhibitors may be at increased risk for angioedema.</p> <p>Older adult patients should be closely monitored, and doses should be adjusted for adverse reactions.</p> <p>The drug is available in blister packs.</p> <p>Women of reproductive potential should use contraception during treatment and for at least 8 weeks following completion of therapy. Males with female partners of reproductive potential should use effective contraception during treatment and for 4 weeks after completion of therapy.</p> <p>(Novartis Pharmaceuticals, 2021a)</p> |

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**TABLE 8-1.** Targeted Therapies (*Continued*)

| Drug                                  | Mechanism of Action                                                                                                                                                                                                                                                                                                                                           | Route | Indications                                                                                                             | Side Effects                                                                                                                                                                                                                                          | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
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| Fedratinib<br>(Inrebic <sup>®</sup> ) | Kinase inhibitor with activity against wild-type and variant activated JAK2 and FLT3; JAK2-selective inhibitor with higher inhibitory activity for JAK2 over other family members JAK1, JAK3, and tyrosine kinase inhibitor 2 (TYK2); abnormal activation of JAK2 associated with myeloproliferative neoplasms, including myelofibrosis and polycythemia vera | PO    | Intermediate-2 or high-risk primary or secondary (postpolycythemia vera or postessential thrombocythemia) myelofibrosis | Common: diarrhea, nausea, anemia, vomiting<br>Black box warning: serious and fatal encephalopathy (e.g., Wernicke encephalopathy)<br>Other severe adverse events: hepatotoxicity, anemia, thrombocytopenia, amylase and lipase elevation, GI toxicity | <p>Patients take once daily, with or without food, if baseline platelet count <math>\geq 50,000/\text{mm}^3</math>.</p> <p>Administration with a high-fat meal may reduce the incidence of nausea and vomiting.</p> <p>If patients miss a dose, they should skip the missed dose and take the usual dose the following day.</p> <p>Dose modifications exist for severe renal impairment (CrCl 15–29 ml/min). Avoid use in severe hepatic impairment.</p> <p>Drug interactions exist with strong CYP3A4 inhibitors, strong and moderate CYP3A4 inducers, and dual CYP3A4 and CYP2C19 inhibitors.</p> <p>Consider providing prophylactic antiemetic therapy (e.g., 5-HT<sub>3</sub> receptor antagonist) during treatment. Treat diarrhea with antidiarrheal promptly at the first onset of symptoms.</p> <p>Monitor thiamine levels prior to initiation, periodically during treatment, and as clinically indicated. Do not start in patients with thiamine deficiency. Replete thiamine prior to treatment initiation. If encephalopathy is suspected, immediately discontinue, and initiate parenteral thiamine.</p> <p>Monitor CBC, SCr, blood urea nitrogen, hepatic panel, amylase, and lipase prior to initiation, periodically during treatment, and as clinically indicated.</p> <p>No data exist for drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.</p> <p>(Celgene, 2019)</p> |

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**TABLE 8-1.** Targeted Therapies (Continued)

| Drug                             | Mechanism of Action                                                                                                                                                                                                           | Route | Indications                                                                                                       | Side Effects                                                                                                                                                          | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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| Gefitinib (Iressa <sup>®</sup> ) | Inhibits EGFR (exon 19 deletion and exon 21-point variant L858R) by inhibiting autophosphorylation of tyrosine kinase associated with EGFR, inhibiting further downstream signaling and blocking EGFR-dependent proliferation | PO    | Metastatic NSCLC with EGFR exon 19 deletions or exon 21 (L858R) substitution alterations, as first-line treatment | Common: skin reactions, diarrhea<br>Severe: ILD, hepatotoxicity, GI perforation, diarrhea, ocular disorders (e.g., keratitis), bullous and exfoliative skin disorders | <p>Patients should take once daily with or without food.</p> <p>If patients miss a dose, they should not take the missed dose within 12 hours of the next dose.</p> <p>For patients who have difficulty swallowing solids, immerse gefitinib in 4–8 oz of water and stir for approximately 15 minutes. Have patients drink immediately or administer through nasogastric tube. Rinse the container with 4–8 oz of water, and have patients drink immediately or administer through the nasogastric tube.</p> <p>Drug interactions exist with CYP3A4 inhibitors (including grapefruit) or CYP3A4 inducers. Regularly monitor INR in patients receiving warfarin. Monitor for GI bleeding and elevated INR.</p> <p>Drugs that increase gastric pH decrease gefitinib concentrations. Avoid concomitant use if possible. For PPIs, take gefitinib 12 hours after the last dose or 12 hours before the next dose of the PPI. For H<sub>2</sub> antagonists, take gefitinib 6 hours after or 6 hours before H<sub>2</sub> antagonist or an antacid.</p> <p>Monitor LFTs periodically during treatment. Women of reproductive potential should use contraception during treatment and for at least 2 weeks following completion of therapy.</p> <p>(AstraZeneca Pharmaceuticals, 2021a)</p> |

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**TABLE 8-1.** Targeted Therapies (*Continued*)

| Drug                    | Mechanism of Action                                                                                                                                                                                                                                                                                     | Route | Indications                                                         | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
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| Gilteritinib (Xospata®) | TKI of multiple receptor tyrosine kinases, including FLT3; inhibits FLT3 receptor signaling and proliferation in cells exogenously expressing FLT3, including FLT3-ITD, tyrosine kinase domain alterations, FLT3-D835Y, and FLT3-ITD-D835Y, and induces apoptosis in leukemic cells expressing FLT3-ITD | PO    | Relapsed or refractory AML in adult patients with a FLT3 alteration | <p>Common: increased transaminase, myalgia/arthralgia, fatigue/malaise, fever, mucositis, edema, rash, noninfectious diarrhea, dyspnea, nausea, cough, constipation, eye disorders, headache, dizziness, hypotension, vomiting, renal impairment</p> <p>Black box warning: differentiation syndrome (e.g., fever, dyspnea, hypoxia, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain, peripheral edema, hypotension, renal dysfunction)</p> <p>Other severe adverse events: posterior reversible encephalopathy, prolonged QT interval, pancreatitis</p> | <p>Patients should take once daily, with or without food, at the same time each day. Tablets should be taken whole with a glass of water. Tablets should not be opened, crushed, cut, or dissolved.</p> <p>If patients miss a dose, they should take it as soon as possible on the same day and at least 12 hours prior to the next scheduled dose. Patients should return to the normal schedule the following day. Patients should not take 2 doses within 12 hours.</p> <p>Treatment for a minimum of 6 months is recommended to allow time for a clinical response.</p> <p>Drug interactions exist with combined P-gp and strong CYP3A inducers and strong CYP3A inhibitors.</p> <p>Assess CBCs and blood chemistries, including CPK, prior to the initiation, at least once weekly for the first month, once every other week for the second month, and once monthly for the duration of therapy.</p> <p>Perform an ECG prior to initiation of treatment, on days 8 and 15 of cycle 1, and prior to the start of the 2 subsequent cycles. Correct hypokalemia or hypomagnesemia prior to and during treatment.</p> <p>Monitor for differentiation syndrome (2 days after the start and during the first 3 months on treatment). If differentiation is suspected, initiate corticosteroid therapy (dexamethasone 10 mg IV every 12 hours) and hemodynamic monitoring. Administer steroid for a minimum of 3 days.</p> <p>Women of reproductive potential should use effective contraception during treatment and for 6 months following completion of therapy. Men with female partners of reproductive potential should use effective contraception during treatment and for at least 4 months following completion of therapy. (Astellas Pharma, 2019)</p> |

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**TABLE 8-1.** Targeted Therapies (Continued)

| Drug                               | Mechanism of Action                                                                                                                                                                                                                               | Route | Indications                                                                                                                                                                   | Side Effects                                                                                                                                                                                                                                                                                                                                                             | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
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| Glasdegib (Daurismo <sup>®</sup> ) | Inhibits the Hedgehog pathway by binding to and inhibiting Smoothed, a transmembrane protein involved in Hedgehog signal transduction, leading to reduced tumor growth and reduced percentage of CD45-positive/CD33-positive blasts in the marrow | PO    | Newly diagnosed AML, in combination with low-dose cytarabine, in adult patients aged $\geq 75$ years with comorbidities that preclude use of intensive induction chemotherapy | Common: anemia, fatigue, hemorrhage, febrile neutropenia, musculoskeletal pain, nausea, edema, thrombocytopenia, dyspnea, decreased appetite, dysgeusia, mucositis, constipation, rash<br>Black box warning: embryo-fetal toxicity<br>Other severe adverse events: QTc interval prolongation<br>Less common: loose teeth, toothaches, alopecia, QT interval prolongation | <p>Patients should take once daily, with or without food, at the same time each day for 28 days in combination with cytarabine SC on days 1–10 of each 28-day cycle.</p> <p>Administer over a minimum of 6 cycles to allow time for clinical response.</p> <p>Tablets should not be crushed or split.</p> <p>If patients miss a dose, they should take it as soon as possible if <math>&gt; 12</math> hours prior to the next scheduled dose.</p> <p>If patients vomit a dose, they should not take another dose and should wait until the next scheduled dose.</p> <p>Drug interactions exist with strong CYP3A4 inhibitors (including grapefruit), strong and moderate CYP3A4 inducers, and QTc-prolonging drugs.</p> <p>Assess CBC, electrolytes, and renal and liver function prior to treatment initiation and at least once weekly for the first month.</p> <p>Monitor electrolytes and renal function once monthly for the duration of therapy.</p> <p>Obtain CPK levels prior to initiating therapy and as indicated clinically thereafter (e.g., if muscle symptoms are reported).</p> <p>Monitor ECG prior to therapy, approximately 1 week after initiation, and then once monthly for the next 2 months to assess for QTc prolongation. Repeat ECG if abnormal.</p> <p>Advise patients to not donate blood or platelets during treatment and for at least 30 days after the final dose because blood or blood products might be given to women of reproductive potential.</p> <p>Conduct pregnancy testing in women of reproductive potential within 7 days prior to initiation. They should use effective contraception for 30 days following the final dose. Men should use condoms, even after prior vasectomy, with a pregnant partner or a female partner of reproductive potential</p> |

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**TABLE 8-1.** Targeted Therapies (*Continued*)

| Drug                                         | Mechanism of Action                                                                                                                                    | Route | Indications                                                                                                                                                                                                                                                                                                                                           | Side Effects                                                                                                                                                                                                                                              | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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| Glasdegib<br>(Daurismo®)<br>( <i>Cont.</i> ) |                                                                                                                                                        |       |                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                           | during treatment and for 30 days after the final dose. Advise males not to donate semen for at least 30 days after the final dose.<br>(Pfizer, 2020a)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Ibrutinib<br>(Imbruvica®)                    | Inhibits Bruton tyrosine kinase, which is a signaling molecule of the B-cell antigen receptor, leading to inhibition of malignant B-cell proliferation | PO    | Mantle cell lymphoma in patients who have received at least 1 prior therapy<br>CLL/SLL<br>CLL/SLL with 17p deletion<br>Waldenström macroglobulinemia<br>Marginal zone lymphoma in patients who require systemic therapy and have received at least 1 prior anti-CD20–based therapy<br>GVHD after failure of 1 or more prior lines of systemic therapy | Common: thrombocytopenia, diarrhea, fatigue, musculoskeletal pain, neutropenia, rash, anemia, bruising, stomatitis<br>Severe: hemorrhage, infections, cytopenias, cardiac arrhythmias and cardiac failure, hypertension, second primary malignancies, TLS | Patients should take once daily with a glass of water.<br>Capsules should not be opened, broken, or chewed. Tablets should not be chewed, crushed, or cut.<br>If patients miss a dose, they should take it as soon as possible on the same day, with a return to the normal schedule on the next day.<br>Dose modifications are recommended for mild to moderate hepatic impairment (Child-Pugh A and B). Avoid use in severe hepatic impairment (Child-Pugh C).<br>Drug interactions exist with CYP3A inhibitors (including grapefruit, posaconazole, and voriconazole) and CYP3A inducers.<br>Consider withholding the drug for at least 3–7 days before and after surgery.<br>Consider risk and benefits of concomitant anticoagulant or antiplatelet therapy due to increased risk of bleeding.<br>Monitor CBC monthly.<br>Monitor BP during treatment and initiate or adjust antihypertensives throughout treatment.<br>Women of reproductive potential and males with female partners of reproductive potential should use contraception during treatment and for at least 1 month following completion of therapy.<br>(Pharmacyclics & Janssen Biotech, 2020) |

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**TABLE 8-1.** Targeted Therapies (Continued)

| Drug                  | Mechanism of Action                                                                                                                                                                                | Route | Indications                                                                                                                                                                                                                                                                                                                                                                    | Side Effects                                                                                                                                                                                                                                                                                                                            | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
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| Idelalisib (Zydelig®) | Inhibits PI3K-delta, which is expressed in healthy and malignant B cells, leading to apoptosis and inhibited cell proliferation via inhibition of chemotaxis, adhesion, and reduced cell viability | PO    | <p>Relapsed CLL, in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy because of other comorbidities</p> <p>Relapsed follicular B-cell non-Hodgkin lymphoma in patients who have received at least 2 prior systemic therapies</p> <p>Relapsed SLL in patients who have received at least 2 prior systemic therapies</p> | <p>Common: diarrhea, fatigue, nausea, cough, pyrexia, abdominal pain, pneumonia, rash, neutropenia, increased ALT/AST</p> <p>Black box warnings: hepatotoxicity, diarrhea, colitis, pneumonitis, infections, intestinal perforation</p> <p>Other severe adverse events: cutaneous reactions, hypersensitivity reaction, neutropenia</p> | <p>Patients should take twice daily with or without food.</p> <p>Tablets should be swallowed whole.</p> <p>If patients miss a dose by &lt; 6 hours, they should take the missed dose as soon as possible. If a dose is missed by &gt; 6 hours, they should skip the missed dose and take the next dose at the usual time.</p> <p>Drug interactions exist with CYP3A4 inhibitors (including grapefruit), CYP3A4 inducers, and CYP3A4 substrates.</p> <p>Patients should receive PJP prophylaxis.</p> <p>Clinical and laboratory monitoring for CMV infection is recommended in patients with a history of CMV infection or positive CMV serology at the start of treatment.</p> <p>Diarrhea caused by idelalisib responds poorly to antimotility agents. Drug interruption or corticosteroids may be needed to resolve diarrhea.</p> <p>Monitor LFTs prior to initiation, every 2 weeks for the first 3 months, every 4 weeks for the next 3 months, then every 1–3 months thereafter.</p> <p>Monitor CBC at least every 2 weeks for the first 6 months of therapy.</p> <p>Lymphocytosis has been observed in some patients taking idelalisib. It should not be considered progressive disease in the absence of other clinical findings.</p> <p>Women of reproductive potential should use contraception during treatment and for at least 1 month after completion of therapy.</p> <p>Males with female partners of reproductive potential should use contraception during treatment and for at least 3 months after completion of therapy.</p> <p>(Gilead Sciences, 2020)</p> |

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**TABLE 8-1.** Targeted Therapies (*Continued*)

| Drug                         | Mechanism of Action                                                                                                                                                                                                      | Route | Indications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
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| Imatinib mesylate (Gleevec®) | Inhibits BCR-ABL1 tyrosine kinase created by the Ph-positive genetic abnormality, inhibiting proliferation and inducing apoptosis in BCR-ABL1–positive cell lines; also inhibits PDGF, stem cell factor, and KIT (c-KIT) | PO    | <p>Newly diagnosed Ph-positive CML in chronic phase, in adult and pediatric patients</p> <p>Ph-positive CML in blast crisis, accelerated phase, or chronic phase after failure of interferon-alfa therapy</p> <p>Relapsed or refractory Ph-positive ALL</p> <p>Newly diagnosed Ph-positive ALL in pediatric patients, in combination with chemotherapy</p> <p>MDS/myeloproliferative diseases associated with PDGFR gene rearrangements</p> <p>Aggressive systemic mastocytosis without KIT D816V alteration or unknown KIT alteration status</p> <p>Hypereosinophilic syndrome and/or chronic eosinophilic leukemia in patients who have the FIP1L1-PDGFR-alpha fusion kinase or unknown fusion kinase status</p> <p>Unresectable, recurrent, or metastatic dermatofibrosarcoma protuberans</p> <p>KIT-positive unresectable or metastatic malignant GIST</p> <p>Adjuvant treatment of resected KIT–positive GIST</p> | <p>Common: edema, nausea, vomiting, muscle cramps, musculoskeletal pain, diarrhea, rash, fatigue, abdominal pain</p> <p>Severe: edema and fluid retention, neutropenia, thrombocytopenia, anemia, CHF, left ventricular dysfunction, hepatotoxicity, hemorrhage, GI perforations, cardiogenic shock in patients with high eosinophil levels, bullous dermatologic reactions, hypothyroidism, growth retardation (children and preadolescents), TLS, reports of motor vehicle accidents in patients receiving imatinib, renal toxicity</p> | <p>Patients should take with a meal and a full glass of water to minimize GI irritation. Doses of 400 mg or 600 mg should be administered once daily. Doses of 800 mg should be administered as 400 mg twice daily.</p> <p>For patients unable to swallow tablets, tablets may be dissolved in a glass of water or apple juice immediately before administration. Use 50 ml for a 100 mg tablet and 200 ml for a 400 mg tablet.</p> <p>Drug interactions exist with CYP3A4 inhibitors (including grapefruit), CYP3A4 inducers, CYP3A4 and CYP2D6 substrates, and warfarin.</p> <p>Patients requiring anticoagulation should receive low-molecular-weight or standard heparin and not warfarin.</p> <p>Dose modifications are recommended in patients with severe hepatic impairment and moderate (CrCl 20–39 ml/min) or severe renal impairment.</p> <p>Weigh patients frequently and monitor for signs and symptoms of fluid retention.</p> <p>Monitor CBC weekly for the first month, biweekly for the second month, and periodically thereafter. Cytopenias generally occur within the first several months of therapy.</p> <p>Monitor LFTs prior to initiation and monthly thereafter or as clinically indicated.</p> <p>Monitor renal function prior to initiation and during therapy.</p> <p>In patients with high eosinophil levels, consider prophylactic use of systemic steroid for 1–2 weeks concurrently with initiation of imatinib.</p> <p>Women of reproductive potential should use contraception during treatment and for at least 14 days after completion of therapy. Males with female partners of reproductive potential should use contraception during treatment and for at least 3 months after completion of therapy.</p> <p>(Novartis Pharmaceuticals, 2020a)</p> |

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**TABLE 8-1.** Targeted Therapies (Continued)

| Drug                      | Mechanism of Action                                                                                                                        | Route | Indications                                                                                                                     | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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| Infigratinib (Truseltiq®) | Inhibits FGFR signaling and decreases cell proliferation in cancer cell lines with activating FGFR amplifications, variations, or fusions. | PO    | Previously treated, unresectable, locally advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or other rearrangement | <p>Common: nail toxicity, stomatitis, dry eyes, fatigue, alopecia, palmar-plantar erythrodysesthesia, arthralgia, dysgeusia, constipation, abdominal pain, dry mouth, eyelash changes, diarrhea, dry skin, decreased appetite, blurred vision, vomiting, increased creatinine, increased and decreased phosphate, increased LFTs, decreased hemoglobin, increased lipase, increased calcium, decreased lymphocytes, decreased sodium, increased triglycerides, increased urate, decreased platelets, decreased leukocytes, decreased albumin, decreased potassium</p> <p>Severe: ocular toxicity (retinal pigment epithelial detachment), hyperphosphatemia, soft tissue mineralization</p> | <p>Patients should take once daily for 21 consecutive days, followed by 7 days off until disease progression or unacceptable toxicity.</p> <p>Patients should take on an empty stomach at least 1 hour before or 2 hours after food at approximately the same time each day.</p> <p>Capsules should be swallowed whole. They should not be crushed, chewed, or dissolved.</p> <p>If patients miss a dose by <math>\geq 4</math> hours or if vomiting occurs, they should skip the dose and resume the regular daily dose the next day.</p> <p>Dose modifications are recommended for mild to moderate renal or hepatic impairment.</p> <p>Drug interactions exist with strong and moderate CYP3A inhibitors (including grapefruit), strong and moderate CYP3A inducers, and gastric acid-reducing agents. Avoid coadministration if possible. Administer an <math>H_2</math> antagonist 2 hours before or 10 hours after infigratinib and locally acting antacid 2 hours before or after infigratinib.</p> <p>Perform a comprehensive ophthalmologic examination, including optical coherence tomography, prior to initiation and at 1 month, 3 months, and then every 3 months thereafter during treatment.</p> <p>Monitor for hyperphosphatemia throughout treatment. Initiate phosphate lowering therapy when serum phosphate is <math>&gt; 5.5</math> mg/dl.</p> <p>Advise patients to use artificial tear substitutes or hydrating or lubricating eye gels to prevent or treat dry eyes.</p> <p>Women of reproductive potential and males with female partners of reproductive potential should use contraception during treatment and for 1 month after completion of therapy.</p> <p>The drug is available in 21-day blister packs. (QED Therapeutics, 2021)</p> |

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**TABLE 8-1.** Targeted Therapies (*Continued*)

| Drug                   | Mechanism of Action                                                   | Route | Indications                                                                                                                  | Side Effects                                                                                                                                                                                                                                                                | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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| Ixazomib<br>(Ninlaro®) | Reversible proteasome inhibitor leading to apoptosis of myeloma cells | PO    | Multiple myeloma, in combination with lenalidomide and dexamethasone, in patients who have received at least 1 prior therapy | Common: thrombocytopenia, diarrhea, constipation, nausea, vomiting, peripheral neuropathy, peripheral edema, back pain<br>Severe: thrombocytopenia, GI toxicities, peripheral neuropathy, peripheral edema, cutaneous reactions, thrombotic microangiopathy, hepatotoxicity | <p>Patients should take once weekly on days 1, 8, and 15 of a 28-day cycle at approximately the same time and with water. Patients should take on an empty stomach at least 1 hour before or 2 hours after food.</p> <p>Capsules should not be crushed, chewed, or opened. Drug should be stored in the original packaging and not removed until just prior to taking.</p> <p>If patients delay or miss a dose, they should take it if the next scheduled dose is <math>\geq 72</math> hours away. If patients vomit, they should not repeat the dose.</p> <p>Drug interactions exist with CYP3A4 inducers. Dose modifications are recommended in patients with moderate or severe hepatic impairment and severe renal impairment (<math>\text{CrCl} &lt; 30 \text{ ml/min}</math> or dialysis).</p> <p>Assess hematologic parameters prior to initiating a new cycle (<math>\text{ANC} \geq 1,000/\text{mm}^3</math> and platelets <math>\geq 75,000/\text{mm}^3</math>).</p> <p>Monitor CBC at least monthly prior to each cycle. Consider more frequent monitoring during the first 3 cycles.</p> <p>Monitor LFTs periodically.</p> <p>Consider antiviral prophylaxis to decrease risk of herpes zoster reactivation.</p> <p>Hormonal contraceptives may be ineffective when used concurrently (with dexamethasone). Women of reproductive potential should use nonhormonal contraception during treatment and for at least 90 days after completion of therapy. Males with female partners of reproductive potential should use effective contraception during treatment and for at least 90 days after the completion of therapy.</p> <p>(Millennium Pharmaceuticals, 2021)</p> |

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**TABLE 8-1.** Targeted Therapies (Continued)

| Drug                  | Mechanism of Action                                                                                                                                                     | Route | Indications                                                                                                                                                                                                                                                                                        | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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| Ivosidenib (Tibsovo®) | Small molecule inhibitor that targets the altered IDH1 enzyme, inducing myeloid differentiation; reduces blast counts and increases percentages of mature myeloid cells | PO    | Newly diagnosed AML with a susceptible IDH1 alteration in patients aged ≥ 75 years or who have comorbidities that preclude use of intensive induction chemotherapy<br>Relapsed or refractory AML<br>Locally advanced or metastatic cholangiocarcinoma in patients who have been previously treated | Common: fatigue, leukocytosis, arthralgia, diarrhea, dyspnea, edema, nausea, mucositis, QT interval prolongation, rash, fever, cough, constipation, decreased appetite, myalgia, decreased hemoglobin, decreased calcium, decreased sodium, decreased magnesium, increased uric acid, decreased potassium, increased LFTs, decreased phosphate, increased creatinine, increased bilirubin, abdominal pain<br>Black box warning: differentiation syndrome in AML (e.g., fever; dyspnea; hypoxia; pulmonary infiltrates; pleural or pericardial effusions; rapid weight gain; peripheral edema; hypotension; hepatic, renal, or multiorgan dysfunction)<br>Other severe adverse events: QTc prolongation, Guillain-Barré syndrome | Patients should take once daily with or without food.<br>Tablets should not be taken with a high-fat meal because of increased ivosidenib concentration.<br>Tablets should not be split or crushed.<br>If treating AML, treat for a minimum of 6 months to allow time for clinical response.<br>If patients miss a dose, it should be taken as soon as possible if > 12 hours before the next scheduled dose. Patients should not take 2 doses within 12 hours.<br>If patients vomit a dose, they should not take a replacement dose; they should take the next dose at the regular time.<br>Drug interactions exist with strong CYP3A4 inhibitors, strong CYP3A4 inducers, sensitive CYP3A4 substrates, or QTc-prolonging drugs.<br>Assess CBC and blood chemistries prior to initiation, at least once weekly for the first month, once every two weeks for the second month, and once monthly for the duration of therapy.<br>Monitor CPK weekly for the first month.<br>Monitor ECG at least once weekly for the first 3 weeks of therapy then at least once monthly for duration of therapy.<br>Monitor for hypokalemia and hypomagnesemia.<br>If treating AML, monitor for differentiation syndrome 2 days after the start and during the first 3 months of treatment. If differentiation is suspected, initiate corticosteroid therapy (dexamethasone 10 mg IV every 12 hours) and hemodynamic monitoring. (Servier Pharmaceuticals, 2021) |

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**TABLE 8-1.** Targeted Therapies (*Continued*)

| Drug                | Mechanism of Action                                                     | Route | Indications                                                                                                                                                                                                                                                                                                                                                      | Side Effects                                                                                                                                                                         | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
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| Lapatinib (Tykerb®) | Inhibitor of the intracellular tyrosine kinase domains of EGFR and HER2 | PO    | Advanced or metastatic breast cancer that overexpresses HER2, in combination with capecitabine, in patients who have received prior therapy, including an anthracycline, a taxane, and trastuzumab<br>HR-positive metastatic breast cancer that overexpresses HER2, in combination with letrozole, in postmenopausal women for whom hormone therapy is indicated | Common: diarrhea, rash, nausea, fatigue<br>Black box: hepatotoxicity<br>Other severe adverse events: decreased LVEF, diarrhea, ILD/pneumonitis, QT prolongation, cutaneous reactions | <p>Patients should take once daily on an empty stomach at least 1 hour before or after a meal. Do not divide the daily dose. However, capecitabine should be taken with a meal or within 30 minutes after a meal.</p> <p>If patients miss a dose, they should not double the dose the following day.</p> <p>Drug interactions exist with strong CYP3A4 inhibitors (including grapefruit), strong CYP3A4 inducers, and substrates of CYP3A4, CYP2C8, and P-gp.</p> <p>Dose modifications are recommended for patients with severe hepatic impairment (Child-Pugh C).</p> <p>Confirm normal LVEF before initiation and throughout treatment. Lapatinib should be discontinued in patients if LVEF drops below lower limits of normal.</p> <p>Diarrhea may be managed with antidiarrheal agents (e.g., loperamide); replace fluids and electrolytes if severe.</p> <p>Monitor and correct for hypomagnesemia and hypokalemia to reduce risk of QT prolongation.</p> <p>Monitor LFTs prior to initiation, every 4–6 weeks during treatment, and as clinically indicated.</p> <p>Women of reproductive potential and males with female partners of reproductive potential should use effective contraception during treatment and for at least 1 week after completion of therapy.</p> <p>(Novartis Pharmaceuticals, 2020e)</p> |

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**TABLE 8-1.** Targeted Therapies (Continued)

| Drug                      | Mechanism of Action                                                                                                                                                                                                    | Route | Indications                                                                                                                                                                                                                                                                                                                                                                                                         | Side Effects                                                                                                                                                                                                                                                                                                                                                                  | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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| Larotrectinib (Vitrakvi®) | Inhibits TRKs (TRKA, TRKB, and TRKC), which are encoded by the genes <i>NTRK1</i> , <i>NTRK2</i> , and <i>NTRK3</i> , and can act as oncogenic drivers and promote cellular proliferation and tumor cell line survival | PO    | <p>Adult and pediatric patients with solid tumors with the following characteristics:</p> <ul style="list-style-type: none"> <li>• <i>NTRK</i> gene fusion without a known acquired resistance alteration</li> <li>• Metastatic disease or if surgical resection would likely result in severe morbidity</li> <li>• No satisfactory alternative treatment options or have progressed following treatment</li> </ul> | <p>Common: fatigue, nausea, dizziness, vomiting, increased LFTs, cough, anemia, musculoskeletal pain, hypoalbuminemia, neutropenia, leukopenia, constipation, diarrhea, hypocalcemia, pyrexia, lymphopenia, abdominal pain</p> <p>Severe: CNS effects (including dizziness, cognitive impairment, mood disorders, sleep disturbances), skeletal fractures, hepatotoxicity</p> | <p>Patients should take twice daily with or without food</p> <p>For pediatric patients with a BSA &lt; 1 m<sup>2</sup>, dose is BSA-based.</p> <p>The drug is available as a capsule or an oral solution.</p> <p>Capsules should be swallowed whole with water. They should not be crushed or chewed.</p> <p>If patients miss a dose, they should not make up the missed dose if within 6 hours of the next scheduled dose.</p> <p>If patients vomit a dose, they should skip that dose and take the usual dose the following day.</p> <p>If using oral solution, it can be stored in the refrigerator for up to 90 days after opening. Gloves should be worn by the caregiver during preparation and administration.</p> <p>Dose modification is recommended in patients with moderate (Child-Pugh B) to severe (Child-Pugh C) hepatic impairment.</p> <p>Drug interactions exist with strong CYP3A4 inhibitors, strong CYP3A4 inducers, and sensitive CYP3A4 substrates.</p> <p>Monitor for signs of neurotoxicity and advise patients not to drive or operate hazardous machinery if experiencing neurotoxicity.</p> <p>Monitor LFTs every 2 weeks during the first month of treatment, monthly thereafter, and as clinically indicated.</p> <p>Women of reproductive potential and males with female partners of reproductive potential should use effective contraception during treatment and for 1 week following completion of therapy.</p> <p>(Bayer HealthCare, 2021b)</p> |

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**TABLE 8-1.** Targeted Therapies (*Continued*)

| Drug                  | Mechanism of Action                                                                                                                                                              | Route | Indications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
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| Lenvatinib (Lenvima®) | TKI of primarily VEGF receptors, which inhibits angiogenesis, tumor growth, and cancer progression; also inhibits FGFR1, FGFR2, FGFR3, and FGFR4; PDGFR- $\alpha$ , KIT; and RET | PO    | <p>Locally recurrent or metastatic, progressive, radioactive iodine–refractory differentiated thyroid cancer, as a single agent</p> <p>Advanced RCC, in combination with everolimus, following 1 prior antiangiogenic therapy</p> <p>Unresectable HCC, as first-line treatment</p> <p>Advanced endometrial carcinoma that is not microsatellite instability high or mismatch repair deficient, in combination with pembrolizumab, in patients who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation</p> | <p>Common: hypertension, fatigue, diarrhea, arthralgia/myalgia, decreased appetite, decreased weight, nausea, stomatitis, headache, vomiting, proteinuria, palmar-plantar erythrodysesthesia, abdominal pain, dysphonia</p> <p>Severe: hypertension, cardiac dysfunction, arterial thromboembolic events, hepatotoxicity, proteinuria, diarrhea, renal failure and impairment, GI perforation and fistula formation, QT interval prolongation, hypocalcemia, RPLS, hemorrhagic events, thyroid dysfunction, impaired wound healing, osteonecrosis of the jaw</p> | <p>Patients should take once daily at the same time with or without food. Capsule should be swallowed whole or dissolved in a small glass of water or apple juice.</p> <p>Dose modification is recommended for severe renal impairment (<math>\text{CrCl} &lt; 30 \text{ ml/min}</math>) and severe hepatic impairment (Child-Pugh C).</p> <p>Patient instructions for dissolving the drug: Measure 1 tablespoon of water or apple juice and put the capsules into the liquid without breaking or crushing them. Leave the capsules in the liquid for at least 10 minutes. Stir for at least 3 minutes. Drink the mixture. After drinking, add a new tablespoon of liquid to the glass, swirl a few times, and drink the contents.</p> <p>If patients miss a dose and it cannot be taken within 12 hours, they should skip that dose.</p> <p>Drug interactions exist with other drugs that prolong QT interval.</p> <p>Optimize BP prior to treatment and monitor during treatment after 1 week, then every 2 weeks for the first 2 months, then monthly during treatment.</p> <p>Monitor LFTs prior to treatment, every 2 weeks for the first 2 months, then once monthly during treatment.</p> <p>Monitor for proteinuria prior to initiation and periodically during treatment.</p> <p>Monitor blood calcium levels at least monthly and replace calcium as necessary.</p> <p>Monitor thyroid function prior to treatment and monthly during treatment.</p> <p>Hold for at least 1 week before elective surgery and do not administer for at least 2 weeks following major surgery and until adequate wound healing.</p> <p>Consider preventive dentistry prior to treatment. Diarrhea may be managed with antidiarrheal agents (e.g., loperamide) and hydration as needed.</p> <p>Women of reproductive potential should use contraception during treatment and for at least 30 days following completion of therapy. The drug is available as 5-day blister cards. (Eisai, 2021)</p> |

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**TABLE 8-1.** Targeted Therapies (*Continued*)

| Drug                   | Mechanism of Action                                                                                                                       | Route | Indications                                       | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
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| Lorlatinib (Lorbrena®) | TKI targeting ALK and RET to decrease tumor cell viability in cell lines harboring ALK fusions, amplifications, or activating alterations | PO    | Metastatic, ALK-positive NSCLC, as a single agent | <p>Common: edema, peripheral neuropathy, weight gain, cognitive effects, fatigue, dyspnea, arthralgia, diarrhea, mood effects</p> <p>Severe: risk of serious hepatotoxicity with concomitant use of strong CYP3A inducers, CNS effects (e.g., seizures, psychotic effects, changes in cognitive function), mood (e.g., suicidal ideation, mental status), speech, sleep disturbances, hypercholesterolemia, hypertriglyceridemia, cough, ILD/pneumonitis, hypertension, hyperglycemia, atrioventricular block</p> | <p>Patients should take once daily with or without food.</p> <p>Tablets should be swallowed whole and not chewed, crushed, or split.</p> <p>If patients miss a dose, they should take the missed dose unless the next dose is due within 4 hours.</p> <p>If patients vomit a dose, they should not take an additional dose but continue with the next scheduled dose.</p> <p>Dose modifications are recommended for severe renal impairment (CrCl 15 to &lt; 30 mL/min).</p> <p>Drug interactions exist for moderate to strong CYP3A inducers, strong CYP3A inhibitors, CYP3A substrates, P-gp substrates, and fluconazole.</p> <p>Monitor BP after 2 weeks and then at least monthly during treatment. Withhold for severe hypertension.</p> <p>Monitor fasting serum glucose prior to starting and regularly during treatment.</p> <p>Monitor serum cholesterol and triglycerides before initiating treatment, 1 and 2 months after initiation, and periodically thereafter.</p> <p>Monitor ECG at baseline and periodically.</p> <p>CNS effects occurred in more than 50% of patients in clinical trials. Median time to onset of any CNS effect was 1.4 months.</p> <p>Hormonal contraceptives may be ineffective when used concurrently with lorlatinib.</p> <p>Women of reproductive potential should be advised to use nonhormone contraception during treatment and for at least 6 months after the final dose. Males with female partners of reproductive potential should use effective contraception during treatment and for at least 3 months after completing therapy.</p> <p>(Pfizer, 2021b)</p> |

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**TABLE 8-1.** Targeted Therapies (*Continued*)

| Drug                                     | Mechanism of Action                                                                                                                              | Route | Indications                                                                                                                                                                                                                                                                  | Side Effects                                                                                                                                                                                                                                                                                                                                          | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
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| Midostaurin<br>(Rydapt <sup>®</sup> )    | Inhibits multiple receptor tyrosine kinases, primarily FLT3 receptor signaling, inducing apoptosis in FLT3-expressing cells                      | PO    | Newly diagnosed AML that is FLT3 alteration–positive in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation<br>Aggressive systemic mastocytosis<br>Systemic mastocytosis with associated hematologic neoplasm<br>Mast cell leukemia | Common: febrile neutropenia, nausea, mucositis, vomiting, headache, petechiae, musculoskeletal pain, epistaxis, device-related infection, hyperglycemia, QT prolongation, upper respiratory tract infection, edema, abdominal pain, constipation, fever, dyspnea<br>Severe: pulmonary toxicity (ILD/pneumonitis)                                      | Patients should take twice daily, approximately every 12 hours with food. Capsules should not be opened or crushed. For AML, patients should take on days 8–21 of each cycle of induction or consolidation. If patients miss or vomit a dose, they should not make up the dose. They should take the next dose at the usual scheduled time. Drug interactions exist with strong CYP3A4 inhibitors (including grapefruit) and strong CYP3A4 inducers that may alter exposure to midostaurin. Administer a prophylactic antiemetic prior to each dose to reduce risk of nausea and vomiting. Women of reproductive potential and males with female partners of reproductive potential should use contraception during treatment and for at least 4 months following completion of therapy. (Novartis Pharmaceuticals, 2021d) |
| Mobocertinib<br>(Exkivity <sup>™</sup> ) | Kinase inhibitor of EGFR that irreversibly binds to and inhibits EGFR exon 20 insertion alterations at a lower concentration than wild-type EGFR | PO    | Locally advanced or metastatic NSCLC with EGFR exon 20 insertion alterations that has progressed on or after platinum-based chemotherapy                                                                                                                                     | Common: diarrhea, rash, nausea, stomatitis, vomiting, decreased appetite, paronychia, fatigue, dry skin, musculoskeletal pain, decreased red blood cells, decreased lymphocytes, increased creatinine<br>Black box warning: QTc prolongation, including torsades de pointes<br>Other severe adverse events: ILD/pneumonitis, cardiotoxicity, diarrhea | Patients should take once daily with or without food. Capsules should be swallowed whole. They should not be opened, chewed, or dissolved. If patients miss a dose and it has been more than 6 hours, they should skip the dose and take the next dose at the regularly scheduled time. If patients vomit a dose, they should not take an extra dose. Drug interactions exist with moderate and strong CYP3A inhibitors (including grapefruit) and moderate or strong CYP3A inducers. Avoid use with concomitant drugs that increase QTc interval. Monitor ECG at baseline and periodically during treatment. Correct any abnormalities in sodium, potassium, calcium, and magnesium. Monitor LVEF at baseline and during treatment.                                                                                       |

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**TABLE 8-1.** Targeted Therapies (Continued)

| Drug                                   | Mechanism of Action                                                                                                                                  | Route | Indications                                                                                                                                                                                                                                                                                              | Side Effects                                                                                                                                                                                                                                                            | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
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| Mobocertinib<br>(Exkivity™)<br>(Cont.) |                                                                                                                                                      |       |                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                         | Median time to first onset of diarrhea is approximately 5 days. Monitor electrolytes and advise patients to start an antidiarrheal agent at first episode of diarrhea. Hormonal contraceptives may be ineffective when used concurrently with mobocertinib. Females of reproductive potential and males with female partners should use nonhormonal contraception during treatment and for at least 1 month after completion of therapy. (Takeda Pharmaceuticals, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Neratinib<br>(Nerlynx®)                | Intracellular kinase inhibitor that binds to and inhibits autophosphorylation of EGFR, HER2, and HER4 and downstream MAPK and Akt signaling pathways | PO    | Early-stage HER2-positive breast cancer, as extended adjuvant treatment following adjuvant trastuzumab-based therapy<br>Advanced or metastatic HER2-positive breast cancer, in combination with capecitabine, in patients who have received 2 or more prior anti-HER2 regimens in the metastatic setting | Common: diarrhea, nausea, abdominal pain, fatigue, vomiting, rash, stomatitis, decreased appetite, muscle spasms, dyspepsia, increased AST/ALT, nail disorder, dry skin, abdominal distension, weight loss, urinary tract infection<br>Severe: diarrhea, hepatotoxicity | Patients should take once daily at approximately the same time with food. Tablets should not be chewed, crushed, or split. If patients miss a dose, they should not replace the missed dose and should resume with the next scheduled daily dose. A two-week dose escalation may be considered to improve tolerability (week 1: 120 mg daily; week 2: 160 mg daily; week 3 and onward: 240 mg daily). Concomitant use with CYP3A4 inhibitors (including grapefruit) or CYP3A4 inducers may alter exposure to neratinib. Concomitant use with P-gp substrates may alter exposure to the P-gp substrate. Avoid concomitant use with PPIs and H <sub>2</sub> antagonists. Separate by 3 hours from antacid dosing. Dose adjustment is required in patients with severe hepatic impairment. Initiate loperamide with the first dose of neratinib and continue during first 2 cycles (56 days) of treatment. Titrate to 1–2 bowel movements per day. Refer to package insert for specific loperamide prophylaxis dosing recommendations. With severe diarrhea, initiate fluids and electrolytes as needed. Women of reproductive potential should use contraception during treatment and for 1 month following completion of therapy. Men should use contraception during treatment and for 3 months following completion of therapy. (Puma Biotechnology, 2021) |

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**TABLE 8-1.** Targeted Therapies (*Continued*)

| Drug                    | Mechanism of Action                                                                                 | Route | Indications                                                                                                                                                                                                                                                                                                                                                   | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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| Nilotinib<br>(Tasigna®) | Inhibits BCR-ABL1 kinase, PDGFR, KIT, CSF1R, and discoidin domain receptor tyrosine kinase 1 (DDR1) | PO    | Newly diagnosed Ph-positive CML in chronic phase in adult and pediatric patients aged ≥1 year<br>Ph-positive CML in chronic or accelerated phase that is resistant or intolerant to prior therapy, including imatinib, in adults<br>Ph-positive CML in chronic phase that is resistant or intolerant to prior TKI therapy, in pediatric patients aged ≥1 year | Common: nausea, rash, headache, fatigue, pruritus, vomiting, diarrhea, cough, constipation, arthralgia, nasopharyngitis, fever, night sweats, thrombocytopenia, neutropenia, anemia<br>Black box warnings: QT prolongation, sudden death<br>Other severe adverse events: myelosuppression, cardiac and arterial vascular occlusive events, pancreatitis and elevated serum lipase, hepatotoxicity, electrolyte abnormalities (hypophosphatemia, hypokalemia, hyperkalemia, hypocalcemia, hyponatremia), TLS, hemorrhage, fluid retention, effects on growth and development in pediatric patients | Patients should take twice daily, 12 hours apart, without food. Patients should avoid food for at least 2 hours before the dose and 1 hour after each dose. Taking with food increases risk for QT prolongation. Capsules should be swallowed whole with water. For patients unable to swallow capsules, the contents may be mixed in 1 teaspoon of applesauce and taken within 15 minutes. Capsules must be crushed in pharmacy. If patients miss a dose, they should not replace the missed dose. They should resume with the next scheduled daily dose. Dose modifications are recommended for patients with baseline hepatic impairment (Child-Pugh A, B, or C). Drug interactions exist with strong CYP3A4 inhibitors (including grapefruit) and strong CYP3A4 inducers. Avoid use of PPIs. Separate antacids from nilotinib by 2 hours. Administer nilotinib 2 hours before or 10 hours after H <sub>2</sub> antagonists. Avoid concomitant use of drugs known to prolong QT interval. Monitor and correct for hypomagnesemia and hypokalemia to reduce risk of QT prolongation. Do not use in patients with hypokalemia, hypomagnesemia, or long QT syndrome. Obtain ECG at baseline, 7 days after initiation, and periodically (including after any dose adjustments) to monitor QTc. Monitor CBC every 2 weeks for the first 2 months and then monthly thereafter. Monitor serum lipase and LFTs monthly. Monitor phosphorus, potassium, calcium, and sodium levels. Monitor lipid panel and glucose periodically during the first year. Monitor patients for unexpected rapid weight gain, swelling, and shortness of breath. Women of reproductive potential should use contraception during treatment and for 14 days following completion of therapy. (Novartis Pharmaceuticals, 2020d) |

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**TABLE 8-1. Targeted Therapies (Continued)**

| Drug                 | Mechanism of Action                                                                                      | Route | Indications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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| Niraparib (Zejula®)  | Inhibits PARP enzymes, which play a role in DNA repair, leading to DNA damage, apoptosis, and cell death | PO    | Maintenance therapy for recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in patients who had complete or partial response to first-line, platinum-based chemotherapy<br>Maintenance therapy for recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in patients who had a complete or partial response to platinum-based chemotherapy<br>Advanced ovarian, fallopian tube, or primary peritoneal cancer that has been treated with 3 or more prior chemotherapy regimens and is associated with HRD-positive status defined by either a pathogenic or suspected pathogenic <i>BRCA</i> 1/2 alteration or genomic instability and that has progressed more than 6 months after response to previous platinum-based chemotherapy | Common: nausea, thrombocytopenia, anemia, fatigue, constipation, musculoskeletal pain, abdominal pain, vomiting, neutropenia, decreased appetite, leukopenia, insomnia, headache, dyspnea, rash, diarrhea, hypertension, cough, dizziness, acute kidney injury, urinary tract infection, hypomagnesemia<br>Severe: MDS/AML, bone marrow suppression, hypertension and cardiovascular events, posterior reversible encephalopathy allergic reactions to tartrazine | Patients should take once daily at approximately the same time with or without food. Bedtime administration may help with managing nausea.<br>Capsules should not be chewed, crushed, or split.<br>For first-line maintenance treatment, dose is based on weight and platelet count. Nausea and vomiting is very common. Prophylactic antiemetic (i.e., ondansetron) is recommended.<br>If patients miss or vomit a dose, they should skip that dose and take the next dose at the regularly scheduled time.<br>Dose modifications are recommended for patients with moderate hepatic impairment. Monitor CBC weekly for the first month, monthly for next 11 months, and periodically thereafter. Monitor BP and heart rate at least weekly for the first 2 months, monthly for the first year, and periodically thereafter.<br>Women of reproductive potential should use contraception during treatment and for at least 6 months following completion of therapy. (GlaxoSmithKline, 2021) |
| Olaparib (Lynparza®) | Inhibits PARP enzymes, which play a role in DNA repair, leading to DNA damage, apoptosis, and cell death | PO    | Maintenance therapy for advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer with pathogenic or suspected pathogenic germline or somatic <i>BRCA</i> 1/2 alterations (gBRCAm or sBRCAm) in patients who are in complete or partial response to first-line platinum-based chemotherapy<br>Maintenance therapy for recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in patients who are in complete or partial response to platinum-based chemotherapy<br>Maintenance therapy in combination with bevacizumab for advanced epithelial ovarian, fallopian tube,                                                                                                                                                                     | Common: anemia, nausea, fatigue, vomiting, diarrhea, dysgeusia, headache, decreased appetite, cough, leukopenia, neutropenia, thrombocytopenia<br>Severe: MDS/AML, pneumonitis, venous thromboembolic events                                                                                                                                                                                                                                                      | Patients should take twice daily with or without food.<br>Tablets should not be chewed, crushed, dissolved, or split.<br>If patients miss a dose, they should skip that dose and take the next dose at the regularly scheduled time.<br>Nausea and vomiting is very common. A prophylactic antiemetic (e.g., ondansetron) is recommended.<br>Dose adjustment is recommended in patients with moderate renal impairment (CrCl 31–50 ml/min). No data are available for use in severe renal impairment (CrCl ≤ 30 ml/min) or severe hepatic impairment.                                                                                                                                                                                                                                                                                                                                                                                                                                         |

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**TABLE 8-1.** Targeted Therapies (*Continued*)

| Drug                                        | Mechanism of Action | Route | Indications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Side Effects | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
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| Olaparib<br>(Lynparza®)<br>( <i>Cont.</i> ) |                     |       | <p>or primary peritoneal cancer in complete or partial response to first-line platinum-based chemotherapy and is associated with HRD-positive status defined by either a pathogenic or suspected pathogenic <i>BRCA</i> 1/2 alteration and/or genomic instability</p> <p>Advanced ovarian cancer with pathogenic or suspected pathogenic germline <i>BRCA</i> 1/2 alteration in adults who have been treated with 3 or more prior lines of chemotherapy</p> <p>Maintenance therapy for metastatic pancreatic adenocarcinoma with pathogenic or suspected pathogenic germline <i>BRCA</i> 1/2 alteration, as detected by an FDA-approved test, in adults whose disease has not progressed on at least 16 weeks of first-line, platinum-based chemotherapy</p> <p>HER-negative breast cancer with pathogenic or suspected pathogenic gBRCAm that has been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting (Patients with HR-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy.)</p> <p>Metastatic, castration-resistant prostate cancer with pathogenic or suspected pathogenic germline or somatic homologous recombination repair gene alteration that has progressed following prior treatment with enzalutamide or abiraterone</p> |              | <p>Drug interactions exist with moderate to severe CYP3A4 inhibitors (including grapefruit) or strong or moderate CYP3A4 inducers.</p> <p>Do not start treatment until patients have recovered from any hematologic toxicity caused by previous chemotherapy. Monitor CBC at baseline and monthly thereafter. For prolonged hematologic toxicities, hold and monitor CBC weekly until recovery.</p> <p>Women of reproductive potential should use contraception during treatment and for at least 6 months following completion of therapy. Males with female partners of reproductive potential should use effective contraception during treatment and for 3 months following completion of therapy.</p> <p>(AstraZeneca Pharmaceuticals, 2021c)</p> |

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**TABLE 8-1.** Targeted Therapies (Continued)

| Drug                    | Mechanism of Action                                                                             | Route | Indications                                                                                                                                                                                                                                                                                                                                         | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                     | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
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| Osimertinib (Tagrisso®) | Inhibits EGFR by binding irreversibly to certain variant forms (T790M, L858R, exon 19 deletion) | PO    | Metastatic EGFR T790M alteration–positive NSCLC that has progressed on or after EGFR TKI therapy<br>Metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R alteration, as detected by an FDA-approved test, as first-line therapy<br>Adjuvant therapy after tumor resection of NSCLC with EGFR exon 19 deletion or exon 21 L858R alterations | Common: diarrhea, rash, leukopenia, lymphopenia, thrombocytopenia, anemia, neutropenia, musculoskeletal pain, dry skin, nail toxicity, fatigue, cough<br>Severe: ILD/pneumonitis; QTc prolongation; cardiomyopathy, including cardiac failure, chronic cardiac failure, CHF, pulmonary edema, and decreased ejection fraction; keratitis, erythema multiforme and Stevens-Johnson Syndrome, cutaneous vasculitis | <p>Patients should take once daily with or without food.</p> <p>If patients miss a dose, they should skip that dose and take the next dose at the next regularly scheduled time.</p> <p>Adjuvant treatment should be given for up to 3 years.</p> <p>In patients with difficulty swallowing tablets, disperse tablet in 60 ml of noncarbonated water only. Stir until tablet is dispersed into small pieces (the tablet will not completely dissolve) and swallow immediately. Do not crush, heat, or ultrasonicate during preparation. Rinse the container with 120–240 ml water and immediately drink.</p> <p>If administered via nasogastric tube, disperse in 15 ml of water, and use an additional 15 ml to transfer any residue to a syringe. Administer this 30 ml immediately with appropriate water flushes (approximately 30 ml). Use gloves.</p> <p>Drug interactions exist with strong CYP3A4 inducers and other medications that prolong QT intervals.</p> <p>Monitor for signs and symptoms of cardiomyopathy.</p> <p>Assess cardiac status, including LVEF at baseline and during treatment for patients with preexisting cardiac risk factors or patients who develop cardiac signs or symptoms during treatment.</p> <p>Monitor ECG and electrolytes (magnesium and potassium) in patients who have a history or predisposition for QTc prolongation or those taking medications known to prolong QTc interval.</p> <p>Women of reproductive potential should use contraception during treatment and for 6 weeks following completion of therapy. Men with female partners of reproductive potential should use contraception during treatment and for 4 months following completion of therapy.</p> <p>(AstraZeneca Pharmaceuticals, 2020)</p> |

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**TABLE 8-1.** Targeted Therapies (Continued)

| Drug                    | Mechanism of Action                                                                                                                              | Route | Indications                                                                                                                                                                                                                                                                       | Side Effects                                                                                                                                                                                                                                                                                                                                    | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
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| Palbociclib (Ibrance®)  | Inhibits CDK4 and CDK6, leading to reduced cellular proliferation by blocking the progression of the cell cycle from G <sub>1</sub> into S phase | PO    | HR-positive, HER2-negative, advanced or metastatic breast cancer, in combination with an aromatase inhibitor as initial endocrine-based therapy, in postmenopausal women or men, or in combination with fulvestrant in women with disease progression following endocrine therapy | Common: neutropenia, infections, leukopenia, fatigue, nausea, stomatitis, anemia, diarrhea, alopecia, thrombocytopenia, rash, vomiting, decreased appetite, asthenia, fever<br>Severe: neutropenia, ILD/pneumonitis                                                                                                                             | Patients should take once daily at approximately the same time for 21 days followed by 7 days off treatment.<br>Tablets may be taken with or without food. Capsules should be taken with food. Tablets and capsules should not be crushed, split, chewed, or opened.<br>If patients miss a dose, they should skip that dose and take the next dose at the next regularly scheduled time.<br>Pre/perimenopausal patients should also receive a luteinizing hormone-releasing hormone agonist.<br>Dose modifications are recommended for patients with severe hepatic impairment (Child-Pugh C).<br>Drug interactions exist with strong CYP3A inhibitors (including grapefruit), strong CYP3A inducers, and CYP3A substrates.<br>Neutropenia is very common, but febrile neutropenia is uncommon.<br>Monitor CBC prior to the start and at the beginning of each cycle and day 15 of the first 2 cycles.<br>Women of reproductive potential should use contraception during treatment and for 3 weeks following completion of therapy. Men with female partners of reproductive potential should use contraception during treatment and for 3 months following completion of therapy.<br>Tablets are available as a monthly box containing 3 weekly blister packs of 7 tablets each. (Pfizer, 2019a, 2019b) |
| Panobinostat (Farydak®) | Inhibits HDAC, resulting in increased acetylation of histone proteins, inducing cell cycle arrest and/or apoptosis of cells                      | PO    | Multiple myeloma, in combination with bortezomib and dexamethasone, in patients who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent                                                                                                   | Common: diarrhea, fatigue, nausea, peripheral edema, decreased appetite, fever, vomiting, hypophosphatemia, hypokalemia, hyponatremia, increased creatinine, thrombocytopenia, lymphopenia, leukopenia, neutropenia, anemia<br>Black box warnings: severe diarrhea, cardiotoxicities<br>Other severe adverse events: hemorrhage, hepatotoxicity | Patients should take every other day for 3 doses per week (days 1, 3, 5, 8, 10, 12) during weeks 1 and 2 of each 21-day cycle.<br>Patients should take at approximately the same time each day with or without food.<br>Capsules should not be opened, crushed, or chewed.<br>If patients miss a dose beyond 12 hours, they should skip the dose and take the usual dose on the following day. If patients vomit a dose, they should skip the dose and take the usual dose on the following day.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

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**TABLE 8-1.** Targeted Therapies (Continued)

| Drug                                  | Mechanism of Action | Route | Indications | Side Effects | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
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| Panobinostat<br>(Farydak®)<br>(Cont.) |                     |       |             |              | <p>Patients should receive 8 cycles with potential for an additional 8 cycles for a total duration of 16 cycles.</p> <p>Dose modifications are recommended in patients with mild to moderate hepatic impairment. Use should be avoided in patients with severe hepatic impairment.</p> <p>Drug interactions exist with strong CYP3A4 inhibitors (including grapefruit), CYP3A4 inducers, sensitive CYP2D6 substrates, and antiarrhythmic/QT-prolonging drugs.</p> <p>Severe diarrhea occurs in approximately 25% of patients. At the first sign of diarrhea, patients should be treated with antidiarrheal medications (e.g., loperamide). Consider prophylactic antiemetics.</p> <p>Monitor CBC at baseline and at least weekly during treatment. Consider monitoring more frequently in patients aged &gt; 65 years due to increased risk of myelosuppression.</p> <p>Monitor LFTs at baseline and regularly during treatment.</p> <p>Perform ECG at baseline and repeat periodically during treatment as clinically indicated.</p> <p>Monitor electrolytes, including magnesium and potassium, and correct values before treatment. Do not initiate in patients with QTcF &gt; 450 msec.</p> <p>Women of reproductive potential should use contraception during treatment and for 3 months following completion of therapy.</p> <p>Males with female partners of reproductive potential should use contraception during treatment and for 6 months following completion of therapy.</p> <p>The drug is available in blister packs containing 6 tablets.</p> <p>(Novartis Pharmaceuticals, 2016)</p> |

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**TABLE 8-1.** Targeted Therapies (*Continued*)

| Drug                     | Mechanism of Action                                                                                                                                                                                                                                                     | Route | Indications                                                                                   | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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| Pazopanib<br>(Votrient®) | Multi-TKI of VEGFR (1, 2, and 3), PDGFR (alpha and beta), FGFR (1 and 3), KIT, interleukin-2 receptor-inducible T-cell kinase (Itk), lymphocyte-specific protein tyrosine kinase (Lck), and CSF1R (c-Fms), interfering with tumor angiogenesis, growth, and progression | PO    | Advanced RCC<br>Advanced soft tissue sarcoma in patients who have received prior chemotherapy | Common: diarrhea, hypertension, hair and skin color changes (depigmentation), nausea, anorexia, vomiting, fatigue, decreased appetite, tumor pain, dysgeusia, headache, musculoskeletal pain, dyspnea<br>Black box warning: hepatotoxicity<br>Other severe adverse events: QTc prolongation (including torsades de pointes), cardiac dysfunction (decreased LVEF, CHF), hemorrhage, arterial and venous thromboembolism, thrombotic microangiopathy (including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome), ILD/pneumonitis, GI perforation, GI fistula formation, posterior reversible encephalopathy hypertension, hypothyroidism, impaired wound healing, TLS, infection, proteinuria | Patients should take once daily without food at least 1 hour before or 2 hours after a meal. Tablets should not be crushed.<br>If a dose is missed beyond 12 hours, patients should skip the dose and take the usual dose on the following day.<br>Dose modifications are recommended in patients with moderate hepatic impairment. Use is not recommended in severe impairment.<br>Drug interactions exist with strong CYP3A4 inhibitors (including grapefruit), strong CYP3A4 inducers, CYP substrates (e.g., CYP3A4, CYP2D6, CYP2C8), simvastatin, and gastric-acid reducing agents.<br>Concomitant use of PPIs or H <sub>2</sub> antagonists is not recommended; consider use of short-acting antacids separated from pazopanib administration by several hours.<br>Concomitant use with simvastatin may increase risk of ALT elevations. Consider weekly monitoring of LFTs.<br>Measure LFTs at baseline and every 2 weeks for cycles 1–2, once monthly for cycles 3–4, then periodically thereafter. Risk of AST/ALT elevation is highest early in treatment.<br>Use with caution in patients with a history of QT prolongation or concomitantly using other drugs that prolong QT interval. Correct electrolyte abnormalities before treatment.<br>Monitor ECG and electrolytes (e.g., calcium, potassium, magnesium) at baseline and as clinically indicated for patients at high risk for developing QTc prolongation.<br>Monitor LVEF at baseline and periodically in patients at risk for cardiac dysfunction, including previous anthracycline exposure.<br>Monitor BP as clinically indicated. Optimize BP before initiating treatment.<br>Monitor thyroid tests at baseline and during treatment.<br>Monitor urinalysis for proteinuria at baseline and periodically during treatment. |

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**TABLE 8-1.** Targeted Therapies (Continued)

| Drug                                | Mechanism of Action                                                                                                            | Route | Indications                                                                                                                            | Side Effects                                                                                                                                                                                                                                                                                                             | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
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| Pazopanib<br>(Votrient®)<br>(Cont.) |                                                                                                                                |       |                                                                                                                                        |                                                                                                                                                                                                                                                                                                                          | Hold pazopanib at least 7 days prior to planned surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing.<br>Women of reproductive potential and males with female partners of reproductive potential should use contraception during treatment and for 2 weeks following completion of therapy. (Novartis Pharmaceuticals, 2020f)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Pemigatinib<br>(Pemazyre®)          | Small molecule kinase inhibitor targeting FGFR1, FGFR2, FGFR3, and FGFR4 to decrease malignant cell proliferation and survival | PO    | Previously treated unresectable locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or other rearrangement in adults | Common: hyperphosphatemia, hypophosphatemia, alopecia, diarrhea, nail toxicity, fatigue, dysgeusia, nausea and vomiting, constipation, stomatitis, dry eyes, dry mouth, dry skin, decreased appetite, arthralgia, abdominal pain, back pain<br>Severe: ocular toxicity, hyperphosphatemia and soft tissue mineralization | Patients should take once daily with or without food for 14 days, followed by 7 days off therapy, in 21-day cycles.<br>Tablets should not be crushed, chewed, split, or dissolved.<br>Dose modifications are recommended for patients with severe renal impairment (eGFR 15–29 ml/min/1.73 m <sup>2</sup> ) and severe hepatic impairment (total bilirubin > 3 × ULN).<br>If patients miss a dose, it can be taken within 4 hours on the same day. If more than 4 hours have passed, patients should skip that dose and take the next dose at the next regularly scheduled time.<br>Drug interactions exist with moderate and strong CYP3A inducers and moderate and strong CYP3A inhibitors (including grapefruit).<br>Ophthalmic examination, including optical coherence tomography, should be performed prior to initiation of therapy, every 2 months for the first 6 months of treatment, and every 3 months thereafter and urgently at any time for visual symptoms.<br>Monitor for hyperphosphatemia. Median time to onset is 8 days. Initiate a low phosphate diet when serum phosphate level is > 5.5 mg/dl. If levels > 7 mg/dl, initiate phosphate lowering therapy and hold pemigatinib.<br>Women of reproductive potential and males with female partners of reproductive potential should use effective contraception during treatment and for 1 week after completion of therapy. (Incyte, 2021) |

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**TABLE 8-1.** Targeted Therapies (*Continued*)

| Drug                       | Mechanism of Action                                                                                              | Route | Indications                                                                                                                                                         | Side Effects                                                                                                                                                                                                                                                                               | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
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| Pexidartinib<br>(Turalio™) | TKI that inhibits CSF1R, KIT, and FLT3-ITD alteration, preventing proliferation of cell lines dependent on CSF1R | PO    | Symptomatic tenosynovial giant cell tumor associated with severe morbidity or functional limitations and that is not amenable to improvement with surgery in adults | Common: increased lactate dehydrogenase, increased AST, hair color changes, fatigue, eye edema, increased ALT, decreased ANC, increased cholesterol, increased ALP, decreased lymphocytes, decreased hemoglobin, rash, dysgeusia, decreased phosphate<br>Black box warning: hepatotoxicity | <p>Patients should take twice daily without food at least 1 hour before or 2 hours after a snack or meal.</p> <p>Capsules should not be opened, broken, or chewed.</p> <p>If patients vomit or miss a dose, they should skip the missed dose and take the next dose the following day at its scheduled time.</p> <p>Dose modifications are recommended for patients with mild to severe renal impairment (CrCl 15–89 ml/min).</p> <p>Drug interactions exist with moderate or strong CYP3A inhibitors (including grapefruit), strong CYP3A inducers, UGT inhibitors, CYP3A substrates, acid-reducing agents, and other products that cause hepatotoxicity.</p> <p>Use with PPIs should be avoided. Administer 2 hours prior or 10 hours after H<sub>2</sub> antagonists and space from locally acting antacids by at least 2 hours.</p> <p>Monitor LFTs prior to initiation, weekly for the first 8 weeks, every 2 weeks for the next month, then every 3 months thereafter.</p> <p>Women of reproductive potential should use effective contraception during treatment and for 1 month after completion of therapy.</p> <p>Males with female partners of reproductive potential should use effective contraception during treatment and for 1 week after completion of therapy.</p> <p>The drug is available only through a Risk Evaluation and Mitigation Strategies (REMS) program.</p> <p>Prescribers must be trained and certified.</p> <p>Patients must be enrolled in a registry.</p> <p>Pharmacies must be certified.</p> <p>(Daiichi Sankyo, 2021)</p> |

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**TABLE 8-1.** Targeted Therapies (Continued)

| Drug                 | Mechanism of Action                               | Route | Indications                                                                                                                                                                                                                                                                                | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
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| Ponatinib (Iclusig®) | TKI of BCR-ABL1, including T315I-altered BCR-ABL1 | PO    | Chronic phase CML with resistance or intolerance to at least 2 prior kinase inhibitors<br>Accelerated or blast phase CML or Ph-positive ALL in patients for whom no other TKI is indicated<br>T315I-positive CML (chronic, accelerated, or blast phase) or T315I-positive, Ph-positive ALL | Common: hypertension, abdominal pain, rash, constipation, headache, dry skin, fatigue, fever, arthralgia, nausea, diarrhea, fluid retention and edema, pancreatitis/lipase elevation, hemorrhage, anemia, hepatic dysfunction, arterial occlusive events, decreased platelets, decreased ANC<br>Black box warnings: arterial occlusion, venous thromboembolism, heart failure, hepatotoxicity<br>Other severe adverse events: hypertension, pancreatitis, neuropathy, ocular toxicity, hemorrhage, fluid retention, cardiac arrhythmias, myelosuppression, TLS, RPLS, impaired wound healing, GI perforation lipase, vomiting, myalgia, pain in extremities | Patients should take once daily with or without food<br>Tablets should not be crushed, broken, cut, or chewed.<br>If patients miss a dose, they should skip the dose and take the next dose at the regularly scheduled time the next day.<br>Dose should be decreased upon achievement of $\leq 1\%$ BCR-ABL1 International Scale.<br>Dose modifications are recommended in patients with hepatic impairment (Child-Pugh A, B, or C).<br>Drug interactions exist with strong CYP3A inhibitors (including grapefruit) and strong CYP3A inducers.<br>Arterial occlusive events have occurred, including fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, and severe peripheral vascular disease.<br>Monitor CBC every 2 weeks for the first 3 months then monthly or as clinically indicated.<br>Monitor LFTs at baseline, then at least monthly.<br>Monitor BP at baseline and as clinically indicated.<br>Monitor serum lipase every 2 weeks for the first 2 months then monthly thereafter.<br>Conduct comprehensive eye examinations at baseline and periodically during treatment.<br>Hold at least 1 week prior to elective surgery.<br>Do not administer for at least 2 weeks following major surgery and until adequate wound healing.<br>Women of reproductive potential should use contraception during treatment and for 3 weeks following completion of therapy.<br>Ponatinib is available only through a restricted distribution program, including an approved pharmacy.<br>(Ariad Pharmaceuticals & Takeda Pharmaceuticals, 2020) |

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**TABLE 8-1.** Targeted Therapies (*Continued*)

| Drug                      | Mechanism of Action                                                                          | Route | Indications                                                                                                                                                                                                                                                                                                                                                                        | Side Effects                                                                                                                                                                                                                                                                                                   | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
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| Pralsetinib<br>(Gavreto™) | Kinase inhibitor of RET fusions (CCDC6-RET) and variations (RET V804L, RET V804M, RET M918T) | PO    | Metastatic RET fusion–positive NSCLC in adults<br>Advanced or metastatic RET–altered medullary thyroid cancer in adults and pediatric patients aged ≥ 12 years who require systemic therapy<br>Advanced or metastatic RET fusion–positive thyroid cancer in adult and pediatric patients aged ≥ 12 years who require systemic therapy and who are refractory to radioactive iodine | Common: fatigue, constipation, musculoskeletal pain, hypertension, diarrhea, neutropenia, lymphopenia, anemia, thrombocytopenia, hypophosphatemia, hyponatremia, hypocalcemia, increased ALT/AST/ALP<br>Severe: ILD/pneumonitis, hypertension, hepatotoxicity, hemorrhagic events, TLS, impaired wound healing | <p>Patients should take once daily on an empty stomach with no food at least 2 hours before or 1 hour after.</p> <p>If patients miss a dose, they should take it as soon as possible on the same day. Patients should resume the regular daily dose schedule the next day.</p> <p>If patients vomit, another dose should not be taken. Patients should take the next dose at the regularly scheduled time.</p> <p>Drug interactions exist with strong CYP3A inhibitors (including grapefruit), combined P-gp and strong CYP3A inhibitors, and strong CYP3A inducers. Hormonal contraceptives may be ineffective because of decreased exposure when used concurrently with pralsetinib.</p> <p>Optimize BP prior to initiating pralsetinib. Monitor BP at baseline, after 1 week, at least monthly thereafter, and as clinically indicated.</p> <p>Monitor ALT and AST at baseline, every 2 weeks for the first 3 months, then monthly thereafter.</p> <p>Hold for at least 5 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing.</p> <p>Women of reproductive potential should use a nonhormonal contraceptive during treatment and for 2 weeks after completion of therapy. Male patients with female partners of reproductive potential should use effective contraception during treatment and for 1 week following completion of therapy. (Blueprint Medicines, 2021b)</p> |

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**TABLE 8-1.** Targeted Therapies (Continued)

| Drug                    | Mechanism of Action                                                                                                                                                                                  | Route | Indications                                                                                                                                                                                                                                                                                                                                                                                                              | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                                                           | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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| Regorafenib (Stivarga®) | Inhibits multiple membrane-bound and intracellular kinases involved in oncogenesis, tumor angiogenesis, metastasis, and tumor immunity, including RET, VEGFR, KIT, PDGFR, FGFR, RAF, BRAF, and CSF1R | PO    | Metastatic colorectal cancer previously treated with other therapies, including a fluoropyrimidine, oxaliplatin, irinotecan, anti-VEGF therapy, and anti-EGFR therapy (if RAS wild-type)<br>Locally advanced, unresectable, or metastatic GIST following previous treatment with imatinib and sunitinib<br>HCC previously treated with sorafenib                                                                         | Common: pain (including GI and abdominal pain), hand-foot skin reactions, rash, fatigue, diarrhea, decreased appetite, hypertension, infection, dysphonia, hyperbilirubinemia, fever, mucositis, weight loss, nausea<br>Black box warning: hepatotoxicity<br>Other severe adverse events: infections, hemorrhage, GI perforation or fistula, dermatologic toxicities, hypertension, cardiac ischemia and infarction, RPLS, wound healing complications | Patients should take once daily at the same time each day on days 1–21 of a 28-day cycle. It should be taken with a low-fat meal containing < 600 calories and < 30% fat. Tablets should be swallowed whole. If patients miss a dose, they should skip it and take the usual dose on the following day. Drug interactions exist with strong CYP3A4 inhibitors (including grapefruit), strong CYP3A4 inducers, and BCRP substrates. Monitor LFTs at baseline, every 2 weeks for the first 2 months, then at least monthly thereafter. Monitor BP weekly for the first 6 weeks then at least once per cycle. Hold for at least 2 weeks prior to elective surgery. Do not administer for at least 2 weeks after major surgery and until adequate wound healing. Women of reproductive potential and males with female partners of reproductive potential should use contraception during treatment and for 2 months following completion of therapy. Discard any unused tablets 7 weeks after opening the bottle. (Bayer HealthCare Pharmaceuticals, 2020) |
| Ribociclib (Kisqali®)   | Inhibits CDK4 and CDK6, leading to arrest in the G <sub>1</sub> phase of the cell cycle and reduced cell proliferation                                                                               | PO    | HR-positive, HER2-negative advanced or metastatic breast cancer, in combination with an aromatase inhibitor as initial endocrine-based therapy, in pre- or perimenopausal and postmenopausal women<br>HR-positive, HER2-negative advanced or metastatic breast cancer, in combination with fulvestrant as initial endocrine-based therapy or following disease progression on endocrine therapy, in postmenopausal women | Common: neutropenia, nausea, fatigue, diarrhea, leukopenia, alopecia, vomiting, constipation, headache, rash, cough, infections<br>Severe: ILD/pneumonitis, severe cutaneous adverse reactions, QT interval prolongation, hepatobiliary toxicity, neutropenia                                                                                                                                                                                          | Patients should take once daily (preferably in the morning), on days 1–21 followed by 7 days off (28-day cycle) with or without food. Tablets should be swallowed whole. They should not be broken, cracked, or otherwise not intact. If patients vomit or miss a dose, they should skip the dose and take the usual dose on the following day. Dose modification is required in patients with moderate or severe hepatic impairment (Child-Pugh B and C). Drug interactions exist with strong CYP3A4 inhibitors (including grapefruit), strong CYP3A4 inducers, CYP3A4 substrates, and drugs known to prolong QT interval.                                                                                                                                                                                                                                                                                                                                                                                                                             |

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**TABLE 8-1.** Targeted Therapies (*Continued*)

| Drug                                         | Mechanism of Action                                                             | Route | Indications                                                                                     | Side Effects                                                                                                                                                                                                                                                                                                                                      | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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| Ribociclib<br>(Kisqali®)<br>( <i>Cont.</i> ) |                                                                                 |       |                                                                                                 |                                                                                                                                                                                                                                                                                                                                                   | <p>Monitor CBC before initiating treatment and every 2 weeks for the first 2 cycles, at the beginning of each of the 4 subsequent cycles, and as clinically indicated.</p> <p>Monitor ECG at baseline, cycle 1 day 14, and at the beginning of the second cycle. Monitor electrolytes at the beginning of the cycle for 6 cycles and as clinically indicated. Avoid use with tamoxifen due to increased QT prolongation. Do not initiate in patients with QTcF <math>\geq</math> 450 msec.</p> <p>Monitor LFTs at baseline, every 2 weeks for the first 2 cycles, at the beginning of the subsequent 4 cycles, and as clinically indicated.</p> <p>Pre/perimenopausal patients should also receive a luteinizing hormone-releasing hormone agonist.</p> <p>Women of reproductive potential should use contraception during treatment and for 3 weeks following completion of therapy.</p> <p>The drug is available in blister packs containing 14 or 21 tablets.</p> <p>(Novartis Pharmaceuticals, 2020b)</p> |
| Ripretinib<br>(Qinlock®)                     | Inhibits KIT proto-oncogene receptor tyrosine kinase and PDGFR- $\alpha$ kinase | PO    | Advanced GIST in adults previously treated with 3 or more kinase inhibitors, including imatinib | <p>Common: alopecia, fatigue, nausea, abdominal pain, constipation, myalgia, diarrhea, decreased appetite, palmar-plantar erythrodysesthesia, vomiting, increased lipase, decreased phosphate</p> <p>Severe: palmar-plantar erythrodysesthesia, new primary cutaneous malignancies, hypertension, cardiac dysfunction, impaired wound healing</p> | <p>Patients should take once daily at the same time of day with or without food.</p> <p>Tablets should be swallowed whole.</p> <p>If patients miss a dose and if &lt; 8 hours have passed, they should take the missed scheduled dose.</p> <p>If patients vomit a dose, they should skip that dose and resume with next scheduled dose.</p> <p>Drug interactions exist with strong CYP3A inhibitors (including grapefruit) and moderate to strong CYP3A inducers.</p> <p>Optimize BP prior to initiating treatment. Monitor BP throughout treatment.</p> <p>Assess LVEF by echocardiogram or multi-gated acquisition scan prior to initiation and during treatment as indicated.</p> <p>Hold for at least 1 week before elective surgery and for at least 2 weeks after major surgery and until adequate wound healing.</p>                                                                                                                                                                                   |

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**TABLE 8-1.** Targeted Therapies (Continued)

| Drug                                | Mechanism of Action                                                                                                                   | Route | Indications                                                                                                                                                           | Side Effects                                                                                                                                                                                                                                      | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
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| Ripretinib<br>(Qinlock®)<br>(Cont.) |                                                                                                                                       |       |                                                                                                                                                                       |                                                                                                                                                                                                                                                   | Perform dermatologic evaluation when initiating treatment and routinely during treatment. Women of reproductive potential and males with female partners of reproductive potential should use effective contraception during treatment and for at least 1 week following completion of therapy.<br>(Deciphera Pharmaceuticals, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Romidepsin<br>(Istodax®)            | Inhibits HDAC, leading to the accumulation of acetylated histones, inducing cell cycle arrest and apoptosis of some cancer cell lines | IV    | Cutaneous T-cell lymphoma in patients who have received 1 prior systemic therapy<br>Peripheral T-cell lymphoma in patients who have received at least 1 prior therapy | Common: thrombocytopenia, neutropenia, lymphopenia anemia, infections, ECG T-wave changes (QT prolongation), TLS, nausea, fatigue, vomiting, anorexia<br>Severe: thrombocytopenia, neutropenia, lymphopenia, anemia, infections, ECG changes, TLS | Administer IV over 4 hours on days 1, 8, and 15 of a 28-day cycle.<br>The patient-specific dose should be diluted in 500 ml NS and is stable for 24 hours at room temperature.<br>Dose modifications are recommended in patients with moderate or severe hepatic impairment.<br>Drug interactions exist with strong CYP3A4 inhibitors (including grapefruit), strong CYP3A4 inducers, and warfarin. Monitor INR more frequently in patients receiving concurrent warfarin therapy.<br>Estrogen-containing contraceptives may be ineffective because of decreased exposure when used concurrently with romidepsin.<br>Monitor CBC regularly during treatment.<br>Monitor for hepatitis B reactivation in those with prior hepatitis B infection.<br>Consider monitoring ECG in patients at high risk for QT prolongation (e.g., congenital long QT syndrome, history of significant cardiovascular disease, other medications that prolong QT).<br>Correct hypokalemia and hypomagnesemia before administration.<br>Women of reproductive potential should use a nonestrogen-containing contraceptive (i.e., condoms, intrauterine device) during treatment and for 1 month after completion of therapy. Male patients with female partners of reproductive potential should use effective contraception during treatment and for 1 month following completion of therapy.<br>Drug is cytotoxic. Follow hazardous drug handling and disposal procedures.<br>(Celgene, 2021b) |

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**TABLE 8-1.** Targeted Therapies (*Continued*)

| Drug                               | Mechanism of Action                                                                                         | Route | Indications                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Side Effects                                                                                                                                                                                                                                                                                                                                | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
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| Romiplostim (Nplate <sup>®</sup> ) | Binds to and activates the TPO receptor to increase platelet production, a mechanism akin to endogenous TPO | SC    | Thrombocytopenia in patients with chronic immune thrombocytopenic purpura who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy<br>Immune thrombocytopenic purpura lasting for at least 6 months in pediatric patients aged $\geq 1$ year who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy<br>Adult and pediatric patients (including term neonates) acutely exposed to myelosuppressive doses of radiation | Common: arthralgia, dizziness, insomnia, myalgia, pain in extremities, abdominal pain, shoulder pain, dyspepsia, paresthesia, headache<br>Severe: increased risk of progression to AML in patients with MDS, thrombotic/thromboembolic complications, formation of neutralizing antibodies, arthralgia resulting in severe thrombocytopenia | Administer once weekly as an SC injection.<br>Adjust dose based on platelet response. Do not exceed the maximum weekly dose of 10 mcg/kg. Do not dose if platelets exceed 400,000/mm <sup>3</sup> .<br>In adults, use actual body weight at initiation of treatment to calculate the initial dose. Future adjustments are based on changes in platelet counts only (not changes in weight).<br>Calculate the dose and reconstitute with the correct volume of sterile water for injection. Gently swirl and invert the vial to reconstitute. Do not shake during reconstitution; protect reconstituted solution from light. Administer reconstituted solution within 24 hours. The administered volume may be very small. Use a syringe with graduations to 0.01 ml. Discard any unused portions of the vial.<br>If the calculated dose is < 23 mcg, dilute with 0.9% sodium chloride injection and sterile water for injection (see package insert for volume).<br>Treatment should only be used in patients whose degree of thrombocytopenia and clinical condition increase the risk for bleeding. Do not use to normalize platelet counts.<br>Obtain CBCs, including platelet counts, weekly during the dose adjustment phase of therapy, then monthly following establishment of a stable dose. Obtain CBCs, including platelet counts, weekly for at least 2 weeks following discontinuation of romiplostim.<br>The drug may cause fetal harm when administered to a pregnant woman.<br>(Amgen, 2021a) |

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**TABLE 8-1.** Targeted Therapies (Continued)

| Drug                 | Mechanism of Action                                                                                 | Route | Indications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Side Effects                                                                                                                                                                                                                                                  | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
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| Rucaparib (Rubraca®) | Inhibits PARP, which plays a role in DNA repair, resulting in DNA damage, apoptosis, and cell death | PO    | Maintenance treatment for recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in a complete or partial response to platinum-based chemotherapy<br>Deleterious BRCA alteration (germline and/or somatic)–associated epithelial ovarian, fallopian tube, or primary peritoneal cancer that has been treated with 2 or more prior lines of chemotherapy<br>Pathogenic BRCA alteration (germline and/or somatic)–associated metastatic castration-resistant prostate cancer who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy | Common: nausea, fatigue, vomiting, anemia, abdominal pain, dysgeusia, constipation, decreased appetite, diarrhea, dyspnea, increased AST/ALT, thrombocytopenia, neutropenia, stomatitis, nasopharyngitis/upper respiratory infection, rash<br>Severe: MDS/AML | Patients should take twice daily (approximately 12 hours apart) with or without food. If patients miss or vomit a dose, they should skip the dose and take the next scheduled dose.<br>Drug interactions exist with CYP1A2, CYP3A, CYP2C9 (e.g., warfarin), and CYP2C19 substrates.<br>Advise patients to use appropriate sun protection because of increased susceptibility to sunburn.<br>Monitor CBC at baseline and monthly thereafter. Do not start until patients have recovered from hematologic toxicity caused by previous chemotherapy.<br>Patients receiving rucaparib for prostate cancer should also receive a gonadotropin-releasing hormone analog concurrently or should have had bilateral orchiectomy.<br>Women of reproductive potential should use contraception during treatment and for 6 months following completion of therapy. (Clovis Oncology, 2020) |

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**TABLE 8-1.** Targeted Therapies (Continued)

| Drug                  | Mechanism of Action                                                                                                  | Route | Indications                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Side Effects                                                                                                                                                                                                                                                                                          | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
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| Ruxolitinib (Jakafi®) | Inhibits JAK1 and JAK2, which mediate cytokines and growth factors responsible for hematopoiesis and immune function | PO    | Intermediate- or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis, and post-essential thrombocythemia myelofibrosis<br>Polycythemia vera in patients with an inadequate response or intolerance to hydroxyurea<br>Steroid-refractory acute GVHD in adult patients and pediatric patients aged $\geq 12$ years<br>Chronic GVHD after failure of 1 or 2 lines of systemic therapy in adult and pediatric patients aged $\geq 12$ years | Common: thrombocytopenia, anemia, bruising, dizziness, headache, edema<br>Severe: thrombocytopenia, anemia, neutropenia, infections (e.g., tuberculosis, herpes zoster, hepatitis B), nonmelanoma skin cancer, hyperlipidemia, risk of symptom exacerbation following interruption or discontinuation | Patients should take twice daily with or without food.<br>If patients miss a dose, they should skip the dose and take the next scheduled dose.<br>If patients are unable to swallow the tablets, ruxolitinib may be administered via nasogastric tube (8 French or greater). Suspend 1 tablet in 40 ml of water and stir for 10 minutes before administration via nasogastric tube, followed by a flush with 75 ml of water. Administer the suspension within 6 hours of preparation.<br>Dose modifications may be necessary in patients with moderate or severe hepatic or renal impairment.<br>Drug interactions exist with strong CYP3A4 inhibitors (including grapefruit) or fluconazole. Avoid use in patients receiving fluconazole doses $> 200$ mg daily, except in patients with acute GVHD.<br>Monitor CBC every 2–4 weeks until the dose is stabilized, then as needed.<br>Based on indication, duration of therapy, and CBC results, doses may be increased or decreased.<br>When discontinuing therapy for reasons other than thrombocytopenia, a gradual taper by 5 mg twice daily each week should occur. Sudden interruption of therapy can lead to symptom exacerbation.<br>Consider tapering the dose after 6 months of treatment in patients with GVHD who have discontinued therapeutic doses of corticosteroids.<br>Perform periodic skin examinations.<br>Assess lipid parameters approximately 8–12 weeks following initiation and as needed. (Incyte, 2020) |

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**TABLE 8-1.** Targeted Therapies (Continued)

| Drug                | Mechanism of Action                                                                                                                                                                                                | Route | Indications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Side Effects                                                                                                                                                                                                                                                                                                                                                                     | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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| Selinexor (Xpovio™) | Inhibits exportin 1 (XPO1), which leads to accumulation of tumor suppressor proteins in the nucleus, reductions in several oncoproteins (e.g., c-myc, cyclin D1), cell cycle arrest, and apoptosis of cancer cells | PO    | <p>Multiple myeloma, in combination with bortezomib and dexamethasone, in patients who have received at least 1 prior therapy</p> <p>Relapsed or refractory multiple myeloma, in combination with dexamethasone, in patients who have received at least 4 prior therapies and whose disease is refractory to at least 2 proteasome inhibitors, at least 2 immunomodulatory agents, and an anti-CD38 monoclonal antibody</p> <p>Relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified, including diffuse large B-cell lymphoma arising from follicular lymphoma, in adults who have received at least 2 lines of systemic therapy</p> | <p>Common: thrombocytopenia, fatigue, nausea, anemia, decreased appetite, decreased weight, diarrhea, vomiting, hyponatremia, neutropenia, leukopenia, constipation, dyspnea, upper respiratory tract infection</p> <p>Severe: thrombocytopenia, neutropenia, GI toxicity (e.g., nausea, vomiting, diarrhea), hyponatremia, serious toxicity, neurologic toxicity, cataracts</p> | <p>Patients should take once to twice weekly depending on the specific regimen. Take at approximately the same time of day. Tablets should be swallowed whole with water and not be crushed, chewed, or split. If patients vomit or miss a dose, they should skip the missed dose and take the usual dose the following day.</p> <p>Monitor CBC, standard blood chemistry, and body weight at baseline and during treatment as clinically indicated. Monitor more frequently during the first 3 months of treatment.</p> <p>Monitor serum sodium levels at baseline, during treatment, and as clinically indicated. Correct for concurrent hyperglycemia and high serum paraprotein levels.</p> <p>Advise patients to avoid taking with other medications that may cause dizziness or confusion because of risk for neurotoxicity. Avoid situations in which dizziness or a confused state may be a problem. Optimize hydration status, CBC, and concomitant medications to avoid dizziness or confusion.</p> <p>Advise patients to take a 5-HT<sub>3</sub> antagonist and/or other antiemetic agents prior to each dose and during treatment.</p> <p>Advise patients to maintain adequate fluid and caloric intake throughout treatment.</p> <p>Women of reproductive potential and males with female partners of reproductive potential should use effective contraception during treatment and for 1 week following completion of therapy.</p> <p>The drug is available as blister packs with various tablet strengths and quantities. (Karyopharm Therapeutics, 2021)</p> |

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**TABLE 8-1.** Targeted Therapies (*Continued*)

| Drug                        | Mechanism of Action                        | Route | Indications                                                                                                                                                                                                                                                                                                                                                                                                                         | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                          | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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| Selpercatinib<br>(Retevmo™) | Inhibits RET, as well as VEGFR1 and VEGFR3 | PO    | Metastatic RET fusion–positive NSCLC in adults<br>Advanced or metastatic RET-variant medullary thyroid cancer in adults and pediatric patients aged ≥ 12 years who require systemic therapy<br>Advanced or metastatic RET fusion–positive thyroid cancer in adults and pediatric patients aged ≥ 12 years who require systemic therapy and whose disease is refractory to radioactive iodine (if radioactive iodine is appropriate) | Common: increased ALT/AST, increased glucose, decreased leukocytes, decreased albumin, decreased calcium, dry mouth, diarrhea, increased creatinine, increased ALP, hypertension, fatigue, edema, decreased platelets, increased total cholesterol, rash, decreased sodium, constipation<br>Severe: hepatotoxicity, hypertension, QT interval prolongation, hemorrhage, hypersensitivity, impaired wound healing, TLS | Patients should take twice daily, approximately every 12 hours, with or without food. Take with food if patients are also on a PPI. The dose is based on weight. Capsules should not be crushed or chewed. If patients miss a dose, they should only take it if it is > 6 hours until next scheduled dose. If patients vomit a dose, they should take the next dose at the regularly scheduled time. Dose modification is recommended for patients with severe hepatic impairment. Monitor ALT and AST at baseline, every 2 weeks during the first 3 months, monthly thereafter, and as clinically indicated. Monitor BP after 1 week, monthly thereafter, and as clinically indicated. Optimize BP prior to initiation. Monitor QT interval, electrolytes (e.g., potassium, magnesium, calcium), and thyroid-stimulating hormone at baseline and periodically during treatment. Withhold for at least 7 days before surgery. Do not administer for at least 2 weeks after major surgery and until adequate wound healing. Drug interactions exist with strong and moderate CYP3A inhibitors, strong and moderate CYP3A inducers, CYP2C8 and CYP3A substrates, and acid-reducing agents. If acid-reducing agent cannot be avoided, take PPI with food; take drug 2 hours before or 10 hours after administration of H <sub>2</sub> receptor antagonist or space 2 hours from locally acting antacid. If hypersensitivity occurs, hold drug and start prednisone 1 mg/kg daily or equivalent. Women of reproductive potential and males with female partners of reproductive potential should use effective contraception during treatment and for 1 week after completion of therapy.<br>(Eli Lilly and Company, 2021b) |

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**TABLE 8-1.** Targeted Therapies (Continued)

| Drug                       | Mechanism of Action    | Route | Indications                                                                                                        | Side Effects                                                                                                                                                                                                                                                                                                          | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
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| Selumetinib<br>(Koselugo™) | Inhibits MEK1 and MEK2 | PO    | Neurofibromatosis type 1 with symptomatic, inoperable plexiform neurofibromas in pediatric patients aged ≥ 2 years | Common: vomiting, rash, abdominal pain, diarrhea, nausea, dry skin, fatigue, musculoskeletal pain, fever, acneiform rash, stomatitis, headache, paronychia, pruritus<br>Severe: cardiomyopathy, ocular toxicity, GI toxicity, rash, increased CPK and rhabdomyolysis, increased vitamin E levels and risk of bleeding | <p>Patients should take twice daily on an empty stomach. They should not eat food for 2 hours before and 1 hour after each dose. Capsules should not be chewed, dissolved, or opened.</p> <p>If patients miss a dose, they should only take it if it is &gt; 6 hours until the next scheduled dose.</p> <p>If patients vomit a dose, they should take the next dose at the regularly scheduled time. Dose modifications are recommended for patients with moderate hepatic impairment (Child-Pugh B).</p> <p>Drug interactions exist with moderate to strong CYP3A4 inhibitors (including grapefruit), fluconazole, and moderate to strong CYP3A4 inducers.</p> <p>Assess LVEF prior to treatment, every 3 months during the first year, every 6 months thereafter, and as clinically indicated.</p> <p>Monitor for ocular toxicities with ophthalmic assessments prior to treatment, at regular intervals, and with new or worsening visual changes.</p> <p>An antidiarrheal agent (e.g., loperamide) should be initiated immediately after the first episode of loose stool. Patients should increase fluid intake.</p> <p>Monitor CPK prior to therapy, periodically during treatment, and when clinically indicated. Selumetinib capsules contain large quantities of vitamin E. Monitor for bleeding.</p> <p>Women of reproductive potential and males with female partners of reproductive potential should use effective contraception during treatment and for 1 week following completion of therapy.</p> <p>(AstraZeneca Pharmaceuticals, 2021b)</p> |

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**TABLE 8-1.** Targeted Therapies (*Continued*)

| Drug                    | Mechanism of Action                                                                                                                                                  | Route | Indications                                                                                                                                                           | Side Effects                                                                                                                                                                                                                                                                                                                                                                                    | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
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| Sonidegib<br>(Odomzo®)  | Inhibits Hedgehog pathway by binding to and inhibiting Smoothened, a transmembrane protein involved in Hedgehog signal transduction                                  | PO    | Locally advanced basal cell carcinoma that has recurred following surgery or radiation therapy or in patients who are not candidates for surgery or radiation therapy | Common: musculoskeletal pain, muscle spasms, alopecia, dysgeusia, fatigue, nausea, diarrhea, weight loss, decreased appetite, myalgia, abdominal pain, headache, pain, vomiting, pruritus<br>Black box warning: embryo-fetal toxicity<br>Other severe adverse events: musculoskeletal adverse reactions                                                                                         | Patients should take once daily on an empty stomach at least 1 hour before or 2 hours after a meal.<br>If patients miss a dose, they should resume dosing with the next scheduled dose.<br>Drug interactions exist with moderate to strong CYP3A inhibitors (including grapefruit) and moderate to strong CYP3A inducers.<br>Advise patients to not donate blood for at least 20 months after the final dose.<br>Monitor creatine kinase and SCr levels at baseline, periodically during treatment, and as clinically indicated.<br>The drug may cause embryo-fetal death or severe birth defects when administered to a pregnant woman. Verify pregnancy status prior to starting therapy. Women of reproductive potential should use contraception during treatment and for 20 months following completion of therapy. Males with female partners of reproductive potential should use contraception during treatment and for 8 months following completion of therapy. (Sun Pharmaceutical Industries, 2019) |
| Sorafenib<br>(Nexavar®) | Inhibits multiple kinases (including C-RAF, BRAF, KIT, FLT3, RET, VEGFR, and PDGFR-beta) thought to be involved in tumor cell signaling, angiogenesis, and apoptosis | PO    | Unresectable HCC<br>Advanced RCC<br>Locally recurrent or metastatic, progressive, differentiated thyroid carcinoma refractory to radioactive iodine treatment         | Common: diarrhea, fatigue, infection, alopecia, hand-foot skin reaction, rash, weight loss, decreased appetite, nausea, GI and abdominal pain, hemorrhage, hypertension<br>Severe: cardiac ischemia and/or infarction, hemorrhage, hypertension, dermatologic toxicities, GI perforation, risk of impaired wound healing, QT prolongation, hepatitis, impairment of thyroid-stimulating hormone | Patients should take twice daily without food at least 1 hour before or 2 hours after a meal.<br>Use with carboplatin and paclitaxel is contraindicated in patients with squamous cell lung cancer because of increased mortality risk.<br>Drug interactions exist with CYP3A4 inducers. Sorafenib may increase the activity of warfarin if taken concomitantly. Monitor INR closely. Avoid concomitant medications that prolong QTc interval.<br>Hold for at least 10 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing.<br>Monitor BP weekly for the first 6 weeks then periodically thereafter.                                                                                                                                                                                                                                                                                                                                |

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**TABLE 8-1.** Targeted Therapies (*Continued*)

| Drug                                        | Mechanism of Action                                                                                                                | Route | Indications                                                                                                            | Side Effects                                                                                                                                                                             | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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| Sorafenib<br>(Nexavar®)<br>( <i>Cont.</i> ) |                                                                                                                                    |       |                                                                                                                        |                                                                                                                                                                                          | <p>Monitor ECG and electrolytes (potassium, calcium, magnesium) in patients at increased risk for ventricular arrhythmias.</p> <p>Monitor LFTs regularly.</p> <p>Monitor thyroid-stimulating hormone monthly.</p> <p>Women of reproductive potential should use effective contraception during treatment and for 6 months following completion of therapy. Males with female partners of reproductive potential should use contraception during treatment and for 3 weeks following completion of therapy.</p> <p>(Bayer HealthCare Pharmaceuticals, 2019)</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Sotorasib<br>(Lumakras™)                    | Inhibits KRAS G12C, leading to blocked KRAS signaling, inhibition of cell growth, and apoptosis only in KRAS G12C tumor cell lines | PO    | KRAS G12C-altered locally advanced or metastatic NSCLC in patients who have received at least 1 prior systemic therapy | <p>Common: diarrhea, musculoskeletal pain, nausea, fatigue, hepatotoxicity, cough, hypocalcemia, hyponatremia, pneumonia, pneumonitis</p> <p>Severe: hepatotoxicity, ILD/pneumonitis</p> | <p>Patients should take once daily at the same time each day with or without food.</p> <p>Tablets should not be chewed, crushed, or split.</p> <p>If patients have difficulty swallowing, tablets may be dispersed in 120 ml (4 oz) of non-carbonated, room temperature water without crushing. Stir until tablets are dispersed into small pieces and drink immediately or within 2 hours. Rinse with an additional 120 ml and drink.</p> <p>If patients miss a dose by &gt; 6 hours, they should take the next dose as prescribed the next day.</p> <p>Drug interactions exist with strong CYP3A4 inducers, CYP3A4 substrates, P-gp substrates, and acid-reducing agents. Avoid coadministration with PPIs and H<sub>2</sub> receptor antagonists. If using a local antacid, administer sotorasib 4 hours before or 10 hours after the antacid.</p> <p>Monitor LFTs every 3 weeks for the first 3 months then once monthly as clinically indicated.</p> <p>Monitor for new or worsening pulmonary symptoms.</p> <p>(Amgen, 2021b)</p> |

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**TABLE 8-1.** Targeted Therapies (*Continued*)

| Drug                | Mechanism of Action                                                                                                                                                          | Route | Indications                                                                                                                                                                                                                                                                    | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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| Sunitinib (Sutent®) | Inhibits multiple receptor tyrosine kinases, including PDGFR, VEGFR, KIT, FLT3, CSF1R, and RET, leading to decreased tumor cell proliferation and reduced tumor angiogenesis | PO    | GIST after disease progression while on imatinib or intolerance to imatinib<br>Advanced RCC<br>Adjuvant treatment of RCC with high risk of recurrence following nephrectomy<br>Progressive, well-differentiated, unresectable, locally advanced, or metastatic pancreatic NETs | Common: fatigue, asthenia, diarrhea, nausea, vomiting, dyspepsia, abdominal pain, hypertension, hand-foot syndrome, altered taste, anorexia, bleeding, mucositis/stomatitis, thrombocytopenia<br>Black box warning: hepatotoxicity<br>Other severe adverse events: cardiovascular events including myocardial ischemia/infarction and left ventricular dysfunction, QT prolongation and torsades de pointes, hypertension, hemorrhagic events, TLS, thrombotic microangiopathy, proteinuria, RPLS, dermatologic toxicities, thyroid dysfunction, hypoglycemia, osteonecrosis of the jaw, impaired wound healing | Patients should take daily with or without food. Schedule for administration varies based on indication.<br>Drug interactions exist with strong CYP3A4 inhibitors (including grapefruit), strong CYP3A4 inducers, and other medications that prolong QTc interval.<br>Consider preventive dentistry prior to treatment. Avoid invasive dental procedures, especially in patients receiving concurrent bisphosphonates. Hold for at least 3 weeks prior to invasive dental procedures.<br>Hold for at least 3 weeks prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing.<br>Monitor LFTs at baseline, during each cycle, and as clinically indicated.<br>Obtain baseline LVEF at baseline and periodically during treatment, especially in patients with cardiac risk factors.<br>Monitor and correct for hypomagnesemia and hypokalemia to reduce risk of QT prolongation. Consider monitoring ECG for patients at high risk for QTc prolongation.<br>Monitor BP at baseline and as clinically indicated.<br>Monitor urine protein, CBC, thyroid function, and serum glucose at baseline and periodically during treatment.<br>Women of reproductive potential should use effective contraception during treatment and for 4 weeks following completion of therapy. Males with female partners of reproductive potential should use contraception during treatment and for 7 weeks following completion of therapy.<br>(Pfizer, 2020c) |

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**TABLE 8-1.** Targeted Therapies (Continued)

| Drug                     | Mechanism of Action                                                                                                                               | Route | Indications                                                                                                                                                                                                                            | Side Effects                                                                                                                                                                                                                                                                      | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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| Talazoparib (Talzenna™)  | Inhibits PARP enzymes, which increases the formation of PARP–DNA complexes and results in DNA damage, decreased cell proliferation, and apoptosis | PO    | Pathogenic or suspected pathogenic germline BRCA-altered, HER2-negative, locally advanced or metastatic breast cancer in adults                                                                                                        | Common: fatigue; anemia; nausea; neutropenia; headache; thrombocytopenia; vomiting; alopecia; diarrhea; decreased appetite; decreased hemoglobin, platelets, ANC, lymphocytes, leukocytes, and calcium; increased glucose, ALT, AST, and ALP<br>Severe: MDS/AML, myelosuppression | Patients should take once daily with or without food.<br>Capsules should be swallowed whole. They should not be opened or dissolved.<br>If patients vomit or miss a dose, they should skip the missed dose and take the usual dose the following day.<br>Dose modifications are recommended for moderate and severe renal impairment (CrCl 15–59 ml/min).<br>Drug interactions exist with P-gp inhibitors and BCRP inhibitors.<br>Monitor CBC at baseline and monthly during treatment and as clinically indicated.<br>Women of reproductive potential should use effective contraception during treatment and for 7 months following completion of therapy. Males with female partners of reproductive potential should use effective contraception during treatment and for 4 months following completion of therapy. (Pfizer, 2020d) |
| Tazemetostat (Tazverik®) | Inhibits EZH2 (methyltransferase) and some EZH2 gain-of-function variants                                                                         | PO    | Metastatic or locally advanced epithelioid sarcoma in adult and pediatric patients aged ≥ 16 years not eligible for complete resection<br>Follicular lymphoma with EZH2 variant in adults who have received at least 2 prior therapies | Common: nausea, decreased appetite, vomiting, constipation, fatigue, upper respiratory tract infection, musculoskeletal pain, abdominal pain<br>Severe: second malignancies (including T-cell lymphoblastic lymphoma, MDS, AML)                                                   | Patients should take twice daily with or without food.<br>Tablets should not be crushed, broken, or split.<br>If patients vomit or miss a dose, they should skip the missed dose and take the dose at the regular time.<br>Drug interactions exist with strong and moderate CYP3A inhibitors (including grapefruit) and strong or moderate CYP3A inducers.<br>Monitor for second primary malignancies, including T-cell lymphoblastic lymphoma, MDS, and AML.<br>Women of reproductive potential should use effective contraception during treatment and for 6 months after completion of therapy. Males with female partners of reproductive potential should use effective contraception during treatment and for at least 3 months after completion of therapy. (Epizyme, 2021)                                                      |

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**TABLE 8-1.** Targeted Therapies (Continued)

| Drug                         | Mechanism of Action                                                                                                                                                                                                                              | Route | Indications                                                              | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                                                        | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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| Tebentafusp-tebn (Kimmtrak®) | Bispecific gp100 peptide; human leukocyte antigen (HLA)-A*02:01-directed T-cell receptor CD3 T-cell engager; activates polyclonal T cells to release inflammatory cytokines and cytolytic proteins, which results in direct lysis of tumor cells | IV    | Unresectable or metastatic uveal melanoma in HLA-A*02:01-positive adults | <p>Common: cytokine release syndrome, rash, fever, pruritus, fatigue, nausea, chills, abdominal pain, edema, hypotension, dry skin, headache, vomiting, decreased lymphocyte count, increased creatinine, increased glucose, increased ALT and AST, decreased hemoglobin, decreased phosphate</p> <p>Black box warning: cytokine release syndrome</p> <p>Other severe adverse events: rash, pruritus, cutaneous edema, elevated liver enzymes</p>   | <p>Select patients for treatment based on a positive HLA-A*02:01 genotyping test.</p> <p>Administer IV over 15–20 minutes once weekly. To prevent adsorption of tebentafusp-tebn to the infusion bag, albumin must be added to the bag (volume of albumin varies based on albumin concentration used).</p> <p>Admixture should be prepared in a 100 ml infusion bag containing NS plus albumin. Administer using a low protein binding 0.2-micron in-line filter.</p> <p>Monitor during the infusion and for at least 16 hours following the first 3 infusions. If patients do not experience <math>\geq</math> grade 2 hypotension during or after the third infusion, subsequent doses may be administered in an appropriate ambulatory care setting. Monitor patients for at least 30 minutes after each infusion.</p> <p>Monitor fluid status, vital signs, and oxygenation level. Ensure patients are euvolemic prior to initiating the infusions.</p> <p>Monitor for skin reactions. The median time to onset of skin reactions was 1 day.</p> <p>Monitor ALT, AST, and total bilirubin prior to start of and during treatment.</p> <p>Women of reproductive potential should use contraception during treatment and for 1 week after the final dose.</p> <p>(Immunocore Limited, 2022)</p> |
| Temsirolimus (Torisel®)      | Kinase that inhibits mTOR, resulting in G <sub>1</sub> growth arrest                                                                                                                                                                             | IV    | Advanced RCC                                                             | <p>Common: rash, asthenia, mucositis, nausea, edema, anorexia, anemia, hypertriglyceridemia, hyperglycemia, hyperlipidemia, elevated ALP, increased SCr, lymphopenia, hypophosphatemia, thrombocytopenia, elevated AST, leukopenia</p> <p>Severe: hypersensitivity reaction, hyperglycemia, hyperlipidemia, hepatic impairment, infections (PJP), ILD, bowel perforation, proteinuria/nephrotic syndrome, renal failure, abnormal wound healing</p> | <p>Administer IV over 30–60 minutes once weekly.</p> <p>Premedicate with prophylactic IV diphenhydramine 25–50 mg (or similar antihistamine) approximately 30 minutes before the start of each dose. Hypersensitivity reaction generally occurs early in the first infusion. To treat, stop infusion and administer an antihistamine (such as diphenhydramine) if not previously administered and/or an H<sub>2</sub> antagonist (IV famotidine or ranitidine) approximately 30 minutes before restarting. Temsirolimus may then be initiated at a lower infusion rate (up to 60 minutes) following a 30–60-minute observation period.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

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**TABLE 8-1.** Targeted Therapies (Continued)

| Drug                                           | Mechanism of Action | Route | Indications | Side Effects | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|------------------------------------------------|---------------------|-------|-------------|--------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>Temsirolimus<br/>(Torisel®)<br/>(Cont.)</p> |                     |       |             |              | <p>Vial content must first be diluted with an enclosed diluent before diluting the resultant solution with 250 ml NS. Prepare temsirolimus in polyvinyl chloride (PVC)-free, non-di(2-ethylhexyl) phthalate (DEHP) glass bottles or infusion bags (polypropylene, polyolefin) and use polyethylene-lined tubing. Protect prepared product from excessive room light and sunlight and administer through an in-line filter of &lt; 5 microns within 6 hours after dilution in NS.</p> <p>Dose modifications are required in patients with mild hepatic impairment, and drug is contraindicated in patients with bilirubin &gt; 1.5 × ULN. Drug interactions exist with strong CYP3A4 inhibitors (including grapefruit) and strong CYP3A4/5 inducers.</p> <p>Angioedema has been reported in combination with angiotensin-converting enzyme inhibitors or calcium channel blockers.</p> <p>Monitor glucose and lipid profiles at baseline and during treatment. Hyperglycemia and hyperlipidemia are likely and may require treatment.</p> <p>Patients with CNS tumors or those receiving additional anticoagulation may be at increased risk for bleeding.</p> <p>Because of the risk for abnormal wound healing, use with caution in the perioperative period.</p> <p>Patients should avoid receiving live vaccines and having close contact with those who have received live vaccines.</p> <p>Older adult patients may be more likely to experience certain adverse reactions, including diarrhea, edema, and pneumonia.</p> <p>Monitor renal function and urine protein at baseline and throughout treatment.</p> <p>Women of reproductive potential and males with female partners of reproductive potential should use contraception during treatment and for 3 months following completion of therapy.</p> <p>Follow hazardous drug special handling and disposal.</p> <p>(Pfizer, 2018)</p> |

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**TABLE 8-1.** Targeted Therapies (*Continued*)

| Drug                     | Mechanism of Action                                                                                                                                | Route | Indications                                                                      | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                                   | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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| Tepotinib<br>(Tepmetko®) | Inhibits MET, including variants with exon 14 skipping, to decrease tumor cell proliferation                                                       | PO    | Metastatic NSCLC with MET exon 14 skipping alterations                           | Common: edema, fatigue, nausea, diarrhea, musculoskeletal pain, dyspnea, decreased lymphocytes, decreased hemoglobin, decreased albumin, decreased sodium, increased gamma glutamyl transferase, increased amylase, increased ALT and AST<br>Severe: ILD/pneumonitis, hepatotoxicity                                                                                                                                           | <p>Patients should take once daily with food. If patients miss a dose, they should take it as soon as possible but not &lt; 8 hours of the next dose.</p> <p>If patients vomit a dose, they should skip the dose and take the next dose at the next regularly scheduled time.</p> <p>Drug interactions exist with strong CYP3A inducers, dual strong CYP3A inhibitors (including grapefruit), P-gp inhibitors, and certain P-gp substrates.</p> <p>Monitor LFTs prior to start of therapy, every 2 weeks for the first 3 months, then once monthly or as clinically indicated.</p> <p>Women of reproductive potential and males with female partners of reproductive potential should use contraception during treatment and for 1 week following completion of therapy.</p> <p>The drug is available in blister cards containing 10 tablets.<br/>(EMD Serono, 2021)</p>                                              |
| Tivozanib<br>(Fotivda®)  | Inhibits VEGFR1, VEGFR2, VEGFR3, and other kinases, including KIT and PDGFR-beta, to inhibit angiogenesis, vascular permeability, and tumor growth | PO    | Relapsed or refractory advanced RCC following 2 or more prior systemic therapies | Common: fatigue, hypertension, diarrhea, decreased appetite, nausea, dysphonia, hypothyroidism, cough, stomatitis, decreased sodium, increased lipase, decreased phosphate<br>Severe: hypertension and hypertensive crisis, cardiac failure, cardiac ischemia, arterial and venous thromboembolic events, hemorrhagic events, proteinuria, thyroid dysfunction, impaired wound healing, RPLS, allergic reactions to tartrazine | <p>Patients should take once daily, with or without food, on days 1–21, followed by 7 days off (28-day cycle).</p> <p>Capsules should be swallowed whole with a glass of water. Capsules should not be opened.</p> <p>If patients miss a dose, they should take the next dose at the regularly scheduled time. They should not take 2 doses at the same time.</p> <p>Dose modifications are recommended for patients with moderate hepatic impairment (total bilirubin &gt; 1.5–3 × ULN).</p> <p>Drug interactions exist with CYP3A inducers. Optimize BP prior to treatment. Monitor BP after 2 weeks of treatment and at least monthly during treatment.</p> <p>Monitor urine protein and thyroid function at baseline and periodically throughout treatment.</p> <p>Hold for at least 24 days before elective surgery. Do not administer for 2 weeks following major surgery and until adequate wound healing.</p> |

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**TABLE 8-1.** Targeted Therapies (Continued)

| Drug                               | Mechanism of Action                                                                                                          | Route | Indications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                             | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
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| Tivozanib<br>(Fotivda®)<br>(Cont.) |                                                                                                                              |       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                          | Women of reproductive potential and males with female partners of reproductive potential should use contraception during treatment and for 1 month following completion of therapy. (Aveo Pharmaceuticals, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Trametinib<br>(Mekinist®)          | Reversible inhibitor of MEK1 and MEK2, which are upstream regulators of the ERK pathway that promotes cellular proliferation | PO    | <p>Unresectable or metastatic melanoma with <i>BRAF</i> V600E or V600K alteration, as a single agent</p> <p>Unresectable or metastatic melanoma with <i>BRAF</i> V600E or V600K alterations, in combination with dabrafenib</p> <p>Metastatic NSCLC with <i>BRAF</i> V600E alteration, in combination with dabrafenib</p> <p>Adjuvant therapy in combination with dabrafenib, for melanoma with <i>BRAF</i> V600E or V600K alterations and involvement of lymph nodes following complete resection</p> <p>Locally advanced or metastatic anaplastic thyroid cancer with <i>BRAF</i> V600E alteration, in combination with dabrafenib, if no satisfactory locoregional treatment options are available</p> | <p>Common: rash, diarrhea, lymphedema, fever, nausea, chills, vomiting, hypertension, peripheral edema, fatigue, dry skin, anorexia, edema, cough, dyspnea</p> <p>Severe: new primary malignancies (cutaneous and noncutaneous), hemorrhage, colitis and GI perforation, venous thromboembolism, cardiomyopathy, ocular toxicities, ILD/pneumonitis, serious febrile reactions, serious skin toxicity, hyperglycemia</p> | <p>Patients should take once daily on an empty stomach at least 1 hour before or 2 hours after a meal.</p> <p>If patients miss a dose, they should not take it if it is within 12 hours of the next dose.</p> <p>Serious febrile reactions can occur when used with dabrafenib. Hold for fever &gt; 104°F or fever accompanied by hypotension, rigors/chills, dehydration, or renal failure. Following the first febrile reaction, administer antipyretics as second prophylaxis. Administer corticosteroids (e.g., prednisone 10 mg daily) for at least 5 days for second or subsequent development of fever if temperature does not return to baseline within 3 days of onset or associated with complications.</p> <p>Monitor patients for new malignancies prior to initiation, during therapy, and following discontinuation.</p> <p>Monitor LVEF at baseline, after 1 month of treatment, then every 2–3 months thereafter.</p> <p>Perform ophthalmologic evaluation for any visual disturbances.</p> <p>Monitor serum glucose levels at baseline and during treatment in patients with preexisting diabetes or hyperglycemia.</p> <p>The drug may interact with radiation and lead to increased CNS, pulmonary, dermatologic, and visceral toxicity. Consider holding ≥ 3 days before and after fractionated radiation and ≥ 1 day before and after stereotactic radiosurgery.</p> <p>Women of reproductive potential should use contraception during treatment and for 4 months following completion of therapy.</p> <p>Store tablets in refrigerator.</p> <p>(National Comprehensive Cancer Network, 2022; Novartis Pharmaceuticals, 2021b)</p> |

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**TABLE 8-1.** Targeted Therapies (*Continued*)

| Drug                   | Mechanism of Action                                                                   | Route | Indications                                                                                                                                                                                                                                       | Side Effects                                                                                                                                                                                                  | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
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| Tucatinib<br>(Tukysa®) | TKI of HER2, resulting in inhibition of MAPK and Akt signaling and cell proliferation | PO    | Advanced unresectable or metastatic HER2-positive breast cancer, in combination with trastuzumab and capecitabine, in patients who have received one or more prior anti-HER2-based regimens in the metastatic setting, including brain metastasis | Common: diarrhea, palmar-plantar erythrodysesthesia, nausea and vomiting, fatigue, hepatotoxicity, stomatitis, decreased appetite, abdominal pain, headache, anemia, rash<br>Severe: diarrhea, hepatotoxicity | <p>Patients should take twice daily, approximately 12 hours apart, with or without food. Tablets should not be chewed, crush, or split. If patients vomit or miss a dose, they should take the next dose at the regularly scheduled time.</p> <p>Dose modifications are recommended for patients with severe hepatic impairment (Child-Pugh C).</p> <p>Drug interactions exist with moderate to strong CYP3A inducers, moderate CYP2C8 inducers, strong CYP2C8 inhibitors, CYP3A substrates, and P-gp substrates.</p> <p>Administer antidiarrheal medications as indicated. Dose of tucatinib may need to be reduced, or treatment may need to be interrupted.</p> <p>Monitor LFTs at baseline, every 3 weeks during treatment, and as clinically indicated. Increased SCr may occur within the first 21 days and persist throughout treatment but is reversible upon treatment completion. Consider alternative markers of renal function if persistent elevation in SCr is observed.</p> <p>Women of reproductive potential and males with female partners of reproductive potential should use effective contraception during treatment and for 1 week after completion of therapy.</p> <p>(Seattle Genetics, 2020)</p> |

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**TABLE 8-1.** Targeted Therapies (Continued)

| Drug                   | Mechanism of Action                                                                                                                                                      | Route | Indications                                                                                                                                                                                                                                 | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                       | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Umbralisib (Ukoniq™)   | Inhibits multiple kinases, including PI3K-delta and casein kinase CK1-epsilon, to inhibit malignant B-cell proliferation                                                 | PO    | Relapsed or refractory marginal zone lymphoma in patients who have received at least 1 prior anti-CD20-based regimen<br>Relapsed or refractory follicular lymphoma in patients who have received at least 3 prior lines of systemic therapy | Common: increased creatinine, diarrhea/colitis, fatigue, nausea, neutropenia, increased ALT/AST<br>Severe: infections, neutropenia, diarrhea or noninfectious colitis, hepatotoxicity, severe cutaneous reactions, allergic reactions due to tartrazine                                                                                                                                                            | Patients should take once daily with food at the same time each day.<br>Tablets should not be crushed, broken, cut, or chewed.<br>If patients miss a dose, they should take it as soon as possible unless it is < 12 hours until the next scheduled dose.<br>If patients vomit a dose, they should not take an additional dose and continue with the next scheduled dose.<br>Administer PJP prophylaxis during treatment. Consider prophylactic antivirals to prevent CMV infection.<br>Monitor CBC with differential at least every 2 weeks for the first 2 months then at least weekly in patients with ANC < 1,000/mm <sup>3</sup> .<br>Monitor LFTs at baseline and during treatment.<br>Women of reproductive potential and males with female partners of reproductive potential should use effective contraception during treatment and for 1 month after completion of therapy.<br>(TG Therapeutics, 2021) |
| Vandetanib (Caprelsa®) | Inhibits multiple kinase families, including VEGFR and EGFR, interfering with oncogenesis, metastasis, tumor angiogenesis, and maintenance of the tumor microenvironment | PO    | Symptomatic or progressive, unresectable, locally advanced or metastatic medullary thyroid cancer                                                                                                                                           | Common: diarrhea/colitis, rash, acneiform dermatitis, hypertension, nausea, headache, upper respiratory tract infection, decreased appetite, abdominal pain<br>Black box warnings: QT prolongation, torsades de pointes, sudden death<br>Other severe adverse events: severe skin reactions, ILD, ischemic cerebrovascular events, hemorrhage, heart failure, diarrhea, hypertension, RPLS, impaired wound healing | Patients should take once daily with or without food.<br>Tablets should not be crushed. If patients are unable to swallow tablets, tablets can be dispersed in 2 oz of water, stirred for approximately 10 minutes, and then swallowed immediately. Any residue in the glass should be mixed with 4 oz of additional water and swallowed. Tablets will not dissolve completely. Dispersion may be administered through nasogastric or gastric tube. Follow hazardous drug handling precautions.<br>If patients miss a dose, they can take the dose up to 12 hours prior to the next dose.<br>Dose modifications are required for moderate or severe renal impairment (CrCl < 50 ml/min). Do not use in patients with moderate or severe hepatic impairment.                                                                                                                                                       |

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**TABLE 8-1.** Targeted Therapies (Continued)

| Drug                                 | Mechanism of Action                                                                                                                                                                                                                         | Route | Indications                                                                                                                       | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|--------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|-----------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Vandetanib<br>(Caprelsa®)<br>(Cont.) |                                                                                                                                                                                                                                             |       |                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | <p>Drug interactions exist with strong CYP3A4 inducers and drugs that may prolong QT interval. It may increase concentrations of digoxin and metformin.</p> <p>Monitor and correct for hypocalcemia, hypomagnesemia, and hypokalemia to reduce risk of QT prolongation.</p> <p>Monitor ECG, electrolytes (potassium, calcium, magnesium), and TSH at baseline, 2–4 weeks, and 8–12 weeks after starting therapy, and every 3 months thereafter.</p> <p>The drug increases sensitivity to sun exposure. Instruct patients to wear sunscreen and protective clothing when exposed to sun during treatment and for 4 months after treatment.</p> <p>Monitor BP regularly during treatment.</p> <p>Hold for at least 1 month prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing.</p> <p>Vandetanib has a long half-life; therefore, adverse reactions may not resolve quickly.</p> <p>Women of reproductive potential should use contraception during treatment and for 4 months following completion of therapy.</p> <p>Vandetanib is available only through a restricted distribution program requiring certification of prescribers and pharmacies. (Sanofi Genzyme, 2020)</p> |
| Vemurafenib<br>(Zelboraf®)           | Inhibits the variant form of BRAF serine/threonine kinase, including <i>BRAF</i> V600E, which is constitutively activated in variant forms, causing cell proliferation in the absence of growth factors normally required for proliferation | PO    | Unresectable or metastatic melanoma with <i>BRAF</i> V600E alteration<br>Erdheim-Chester disease with <i>BRAF</i> V600 alteration | <p>Common: arthralgia, rash, alopecia, pruritus, fatigue, nausea, photosensitivity, skin papilloma</p> <p>Severe: new primary cutaneous malignancies, new noncutaneous squamous cell carcinoma, other malignancies, hypersensitivity reactions, skin reactions, QT prolongation, hepatotoxicity, photosensitivity, serious ophthalmologic reactions, radiation sensitization and recall, renal failure, Dupuytren contracture, plantar fascial fibromatosis</p> | <p>Patients should take twice daily, approximately every 12 hours, with or without food. Tablets should not be crushed or chewed.</p> <p>If patients miss a dose, they can take it up to 4 hours prior to the next dose.</p> <p>If patients vomit a dose, they should take the next dose at the regularly scheduled time.</p> <p>Drug interactions exist with strong CYP3A4 inhibitors (including grapefruit), strong CYP3A4, CYP1A2 substrates, and P-gp substrates.</p> <p>Do not use in wild-type BRAF melanoma because of the risk for increased cell proliferation.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

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**TABLE 8-1.** Targeted Therapies (Continued)

| Drug                                  | Mechanism of Action                                                                                                                                                                                                                                         | Route | Indications                                                                                                                                                                                                            | Side Effects                                                                                                                                                                                       | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
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| Vemurafenib<br>(Zelboraf®)<br>(Cont.) |                                                                                                                                                                                                                                                             |       |                                                                                                                                                                                                                        |                                                                                                                                                                                                    | <p>Perform dermatologic evaluation at baseline, then every 2 months thereafter until 6 months after discontinuation because of the risk of new primary cutaneous malignancies. Dose modifications are required based on the severity of the adverse reaction. Discontinue in patients unable to tolerate at least 480 mg twice daily.</p> <p>Monitor and correct for hypocalcemia, hypomagnesemia, and hypokalemia to reduce risk of QT prolongation. Monitor ECG and electrolytes (potassium, magnesium, calcium) at baseline, 15 days after the start of treatment, monthly during the first 3 months of treatment, and then at least every 3 months thereafter. Avoid use in patients with a QTc &gt; 500 ms and hold therapy if QTc exceeds this time during treatment.</p> <p>Monitor LFTs at baseline and monthly during treatment.</p> <p>Monitor SCr at baseline and periodically during treatment.</p> <p>The drug increases sensitivity to sun exposure. Instruct patients to avoid sun exposure and wear protective clothing and use broad-spectrum sunscreen and lip balm (SPF ≥ 30) when outdoors.</p> <p>Women of reproductive potential should use contraception during treatment and for 2 weeks following completion of therapy. (Genentech, 2020c)</p> |
| Venetoclax<br>(Venclexta®)            | Inhibits B-cell lymphoma 2 protein, an antiapoptotic product; restores apoptosis by binding to B-cell lymphoma 2 protein, displacing proapoptotic proteins (e.g., Bim), triggering mitochondrial outer membrane permeabilization and activation of caspases | PO    | CLL or SLL<br>Newly diagnosed AML, in combination with azacitidine or decitabine or low-dose cytarabine, in adult patients aged ≥ 75 years or with comorbidities that preclude use of intensive induction chemotherapy | <p>Common: neutropenia, anemia, thrombocytopenia, diarrhea, nausea, upper respiratory tract infection, fatigue, cough, musculoskeletal pain, edema</p> <p>Severe: TLS, neutropenia, infections</p> | <p>Patients should take once daily with a meal and water at approximately the same time each day.</p> <p>Tablets should not be chewed, crushed, or broken.</p> <p>The dose should be increased according to a ramp-up schedule (typically over 5 weeks for CLL/SLL and over 3–4 days for AML).</p> <p>If patients miss a dose, they can take it up to 8 hours from the time it is normally taken. If missed by &gt; 8 hours, they should skip that dose and resume with next scheduled dose.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

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| TABLE 8-1. Targeted Therapies (Continued) |                     |       |             |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|-------------------------------------------|---------------------|-------|-------------|--------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Drug                                      | Mechanism of Action | Route | Indications | Side Effects | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Venetoclax<br>(Venclexta®)<br>(Cont.)     |                     |       |             |              | <p>If patients vomit a dose, they should take the next scheduled dose, not an additional dose. Dose modifications are recommended for patients with severe hepatic impairment (Child-Pugh C).</p> <p>Drug interactions exist with moderate to strong CYP3A4 inhibitors (including grapefruit), azole antifungals, moderate to strong P-gp inhibitors, moderate to strong CYP3A4 inducers, and P-gp substrates. Take P-gp substrates at least 6 hours before venetoclax.</p> <p>Concurrent use of CYP3A4 inhibitors during the ramp-up phase is contraindicated. Assess patient risk for TLS. Provide prophylactic hydration and antihyperuricemic (e.g., allopurinol) prior to initiation. Patients with high tumor burden are recommended to be admitted for administration of the first dose of weeks 1 and 2.</p> <p>Patients with AML should have a WBC count &lt; 25,000/mm<sup>3</sup> prior to initiation. Cyto reduction prior to treatment may be required. Patients should be well hydrated during the ramp-up phase to prevent TLS (approximately 56 oz water daily). Patients should drink plenty of water starting 2 days before, on the day of the first dose, and each time the dose is increased.</p> <p>Monitor TLS labs frequently during the first treatment cycle (frequency depends on patient's risk for TLS).</p> <p>Monitor CBC with differential regularly during treatment.</p> <p>Do not administer live attenuated vaccines prior to, during, or after treatment.</p> <p>Women of reproductive potential should use contraception during treatment and for 30 days following completion of therapy.</p> <p>Ramp-up cycle for CLL is available as a starting pack with the first 4 weeks of therapy. (Genentech, 2020b)</p> |

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**TABLE 8-1.** Targeted Therapies (Continued)

| Drug                      | Mechanism of Action                                                                                                                    | Route | Indications                                                                                                                                                                         | Side Effects                                                                                                                                                                                                                                                                    | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|---------------------------|----------------------------------------------------------------------------------------------------------------------------------------|-------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Vismodegib<br>(Erivedge®) | Inhibits the Hedgehog pathway via binding to and inhibiting Smoothed, a transmembrane protein involved in Hedgehog signal transduction | PO    | Metastatic basal cell carcinoma or locally advanced basal cell carcinoma that has recurred following surgery or in patients who are not candidates for surgery or radiation therapy | Common: muscle spasm, alopecia, dysgeusia, weight loss, fatigue, nausea, diarrhea, anorexia, constipation, arthralgia, vomiting, ageusia<br>Black box warning: embryo-fetal toxicity<br>Other severe adverse events: cutaneous adverse reactions, premature fusion of epiphyses | Patients should take once daily with or without food.<br>Capsules should not be crushed or chewed.<br>If patients miss a dose, they should take the next regularly scheduled dose at the usual time.<br>Patients may not donate blood during treatment and for at least 24 months after completing treatment. Men should not donate semen during treatment and for 3 months after therapy.<br>Because of teratogenicity, determine pregnancy status of women of childbearing age within 7 days prior to starting therapy. Inform male patients of fetal risk and instruct on use of contraception during treatment.<br>Women of reproductive potential should use contraception during treatment and for 24 months after completion of therapy. Males with female partners of reproductive potential should use contraception during treatment for 3 months following completion of therapy.<br>(Genentech, 2020a)                                     |
| Vorinostat<br>(Zolinza®)  | Inhibits HDAC, leading to accumulation of acetyl groups on histone lysine residues, resulting in cell cycle arrest and/or apoptosis    | PO    | Cutaneous manifestations of cutaneous T-cell lymphoma in patients who have progressive, persistent, or recurrent disease following 2 systemic therapies                             | Common: fatigue, diarrhea, nausea, thrombocytopenia, anorexia, dysgeusia<br>Severe: pulmonary embolism/deep vein thrombosis, thrombocytopenia, anemia, nausea, vomiting, diarrhea, hyperglycemia, clinical chemistry abnormality (creatinine, magnesium, calcium), GI bleeding  | Patients should take once daily with food.<br>Capsules should not be opened or crushed.<br>Dose modifications are recommended for mild or moderate hepatic impairment.<br>Use with other HDAC inhibitors (e.g., valproic acid) increases the risk for GI bleeding.<br>Use in combination with warfarin may lead to elevated INR. Monitor INR frequently.<br>Patients may require antiemetics, antidiarrheals, fluids, and electrolytes. It is recommended that patients drink 2 L of fluid daily to prevent dehydration.<br>Monitor CBC, glucose, electrolytes, SCr, magnesium, and calcium every 2 weeks for the first 2 months, and monthly thereafter.<br>Women of reproductive potential should use contraception during treatment and for 6 months following completion of therapy. Males with female partners of reproductive potential should use contraception during treatment for 3 months following completion of therapy.<br>(Merck, 2020) |

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**TABLE 8-1.** Targeted Therapies (*Continued*)

| Drug                                  | Mechanism of Action                                                                                                                                                                   | Route | Indications                                                                                                                                                                                                        | Side Effects                                                                                                                                                                                                                                                                                            | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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| Zanubrutinib (Brukinsa <sup>®</sup> ) | Inhibits Bruton tyrosine kinase, which is a signaling molecule of the B-cell antigen receptor and cytokine receptor pathways, leading to inhibition of malignant B-cell proliferation | PO    | Mantle cell lymphoma previously treated with at least 1 prior therapy<br>Waldenström macroglobulinemia<br>Relapsed or refractory marginal zone lymphoma previously treated with at least 1 anti-CD20-based regimen | Common: decreased ANC, lymphocyte, hemoglobin, and platelet counts; upper respiratory tract infection; rash; diarrhea; musculoskeletal pain; increased ALT, increased bilirubin, increased blood uric acid<br>Severe: hemorrhage, infection, cytopenia, second primary malignancies, cardiac arrhythmia | <p>Patients should take once or twice daily (depending on the dose) with or without food.</p> <p>Capsules should be swallowed whole. Capsules should not be opened, broken, or chewed.</p> <p>If patients miss a dose, they should take it as soon as possible on the same day with a return to the normal schedule the following day.</p> <p>Dose modifications are recommended for severe hepatic impairment.</p> <p>Monitor for hemorrhage, infections, cytopenias, second primary malignancies (particularly skin cancer), and cardiac arrhythmia (atrial fibrillation and atrial flutter).</p> <p>Drug interactions exist with moderate or strong CYP3A inhibitors and moderate or strong CYP3A inducers.</p> <p>Monitor CBC regularly during treatment.</p> <p>Asymptomatic lymphocytosis should not be regarded as an adverse effect and patients should continue taking zanubrutinib.</p> <p>Patients should use sun protection.</p> <p>Consider holding 3–7 days presurgery and postsurgery based on risk–benefit analysis.</p> <p>Women of reproductive potential and males with female partners of reproductive potential should use effective contraception for at least 1 week following completion of therapy.</p> <p>(BeiGene, 2021)</p> |

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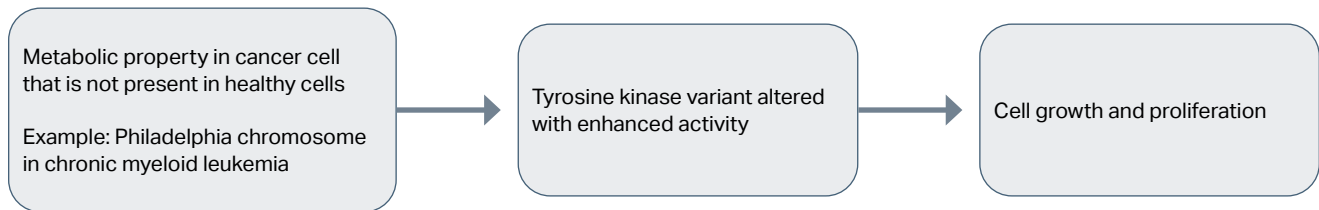


**TABLE 8-1.** Targeted Therapies (Continued)

| Drug                       | Mechanism of Action                                                                                                                                                                                    | Route | Indications                                                                                                                                                                   | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
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| Ziv-aflibercept (Zaltrap®) | Acts as a soluble receptor and binds to VEGF- $\alpha$ , VEGF- $\beta$ , and placental growth factor (known as PlGF), leading to inhibition of neo-vascularization and decreased vascular permeability | IV    | In combination with 5-fluorouracil, leucovorin, and irinotecan (FOLFIR) for metastatic colorectal cancer that is resistant to or progressive during oxaliplatin-based therapy | Common: leukopenia, neutropenia, thrombocytopenia, diarrhea, proteinuria, stomatitis, increased ALT/AST, fatigue, weight loss, anorexia, epistaxis, abdominal pain, dysphonia, elevated SCr, headache<br>Severe: hemorrhage, GI perforation, impaired wound healing, fistula formation, hypertension, arterial thromboembolic events (e.g., transient ischemic attack, cerebrovascular accident, angina), proteinuria, nephrotic syndrome, thrombotic microangiopathy, neutropenia, infection, diarrhea, dehydration, RPLS | Administer infusions over 1 hour through a 0.2-micron polyethersulfone filter prior to any of the other drugs used in the chemotherapy regimen.<br>Do not use with filters made from polyvinylidene fluoride or nylon.<br>Dilute in NS or 5% dextrose in water to a concentration of 0.6–8 mg/ml.<br>Diluted solution may be stored in refrigeration for up to 24 hours and at room temperature for up to 8 hours.<br>Hold dosing at least 4 weeks prior to elective surgery and do not resume for at least 4 weeks following major surgery and until the wound is fully healed.<br>Monitor BP every 2 weeks during treatment or more frequently as clinically indicated. Hold dosing if recurrent or severe hypertension occurs and restart at a lower dose once BP is controlled.<br>Monitor urine protein and hold dosing if proteinuria > 2 g/24 hours; restart once proteinuria < 2 g/24 hours. Dose reduction is recommended for recurrent proteinuria > 2 g/24 hours.<br>Monitor CBC at baseline and prior to each cycle of treatment.<br>Women of reproductive potential should use contraception during treatment and for 1 month following completion of therapy.<br>(Sanofi-Aventis U.S., 2020) |

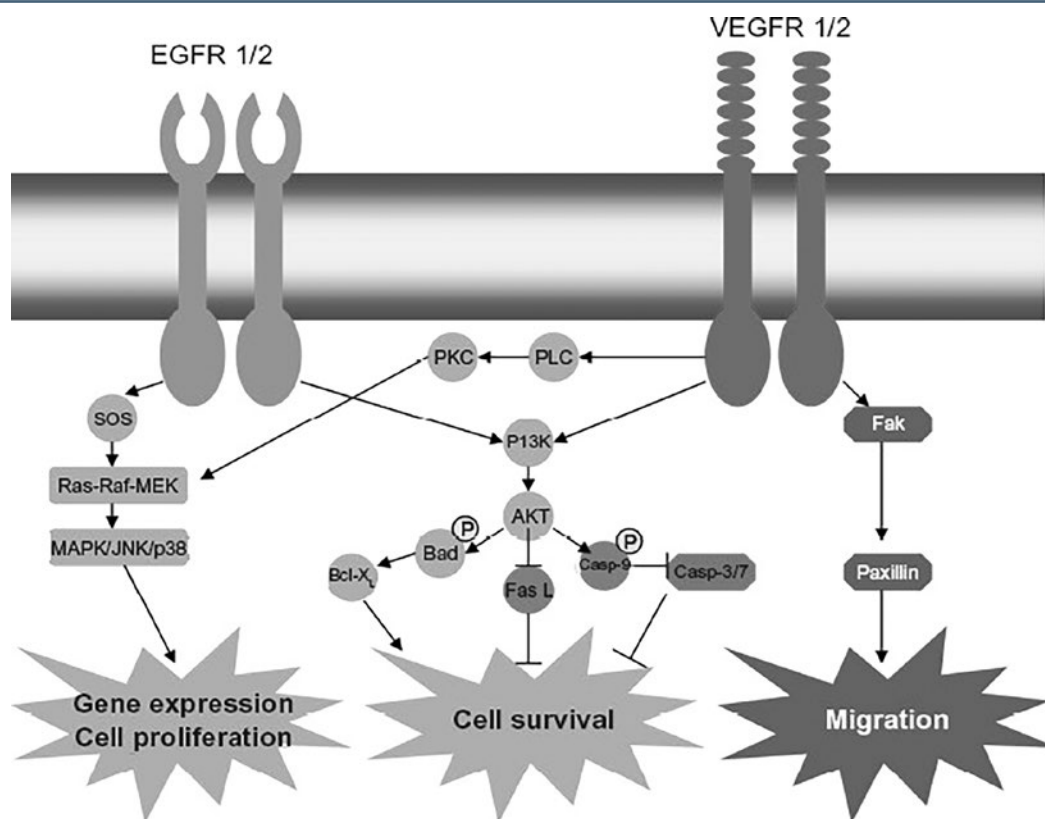
Note. For hazardous oral medications, additional precautions should be taken to prevent exposure when handling or manipulating. Refer to Chapter 12. Review package inserts for dosing and prescribing information.

ABL1—Abelson tyrosine-protein kinase 1; ALCL—anaplastic large cell lymphoma; ALK—anaplastic lymphoma kinase; ALL—acute lymphoblastic leukemia; ALP—alkaline phosphatase; ALT—alanine transaminase; AML—acute myeloid leukemia; ANC—absolute neutrophil count; AST—aspartate transaminase; BCR—breakpoint cluster region protein; BCRP—breast cancer resistance protein; BP—blood pressure; BRCA—breast cancer gene; BSA—body surface area; CBC—complete blood count; CD—cluster of differentiation; CDK—cyclin-dependent kinase; CHF—congestive heart failure; CLL—chronic lymphocytic leukemia; CML—chronic myeloid leukemia; CMV—cytomegalovirus; CNS—central nervous system; CPK—creatine phosphokinase; CrCl—creatinine clearance; CSF1R—colony-stimulating factor 1 receptor; CYP—cytochrome P450; ECG—electrocardiogram; EGFR—epidermal growth factor receptor; ERK—extracellular signal-related kinase; EZH2—enhancer of zeste homolog 2; FDA—U.S. Food and Drug Administration; FGFR—fibroblast growth factor receptor; 5-HT<sub>3</sub>—5-hydroxytryptamine-3; FLT—FMS-like tyrosine kinase; GI—gastrointestinal; GIST—gastrointestinal stromal tumor; GVHD—graft versus host disease; HCC—hepatocellular carcinoma; HDAC—histone deacetylase; HER—human epidermal growth factor receptor; HR—hormone receptor; H<sub>2</sub>—histamine receptor 2; HRD—homologous recombination deficiency; IDH—iscitrate dehydrogenase; ILD—interstitial lung disease; INR—international normalized ratio; ITD—internal tandem duplication; IV—intravenous; JAK—Janus kinase; KRAS—Kirsten rat sarcoma viral oncogene homolog; LFTs—liver function tests; LVEF—left ventricular ejection fraction; MAPK—mitogen-activated protein kinase; MDS—myelodysplastic syndrome; MEK—mitogen-activated extracellular signal regulated kinase; MET—mesenchymal-epithelial transition factor; mTOR—mammalian target of rapamycin; NET—neuroendocrine tumor; NS—normal saline; NSCLC—non-small cell lung cancer; NTRK—neurotrophic tyrosine receptor kinase; PARP—poly(ADP-ribose) polymerase; PDGF—platelet-derived growth factor; PDGFR—platelet-derived growth factor receptor; P-gp—P-glycoprotein; Ph—Philadelphia chromosome; PI3K—phosphoinositide 3-kinase; PJP—*Pneumocystis jirovecii* pneumonia; PO—by mouth; PPI—proton pump inhibitor; RCC—renal cell carcinoma; RET—rearranged during transfection kinase; RON—Recepteur d'Origine Nantais; RPLS—reversible posterior leukoencephalopathy syndrome; SC—subcutaneous; SCr—serum creatinine; SLL—small lymphocytic lymphoma; TKI—tyrosine kinase inhibitor; TLS—tumor lysis syndrome; TPO—thrombopoietin; TRK—tropomyosin receptor tyrosine kinase; UGT—uridine diphosphate-glucuronosyltransferase; ULN—upper limit of normal; VEGF—vascular endothelial growth factor; VEGFR—vascular endothelial growth factor receptor

**FIGURE 8-1.** Basic Principles of Tyrosine Kinases

In cancer cells, a metabolic property is present that is not present in healthy cells. This property leads to enhanced activity of various pathways associated with cellular growth and proliferation.

- (1) The mitogen-activated protein kinase (MAPK) signaling pathway plays an important role in cell proliferation and differentiation.
  - (2) Activation of BRAF within the MAPK pathway leads to downstream signaling of MEK1, MEK2, and extracellular signal-regulated kinases (ERKs).
  - (3) Driver variants in the *BRAF* gene lead to constitutive activation of signaling via this pathway.
  - (4) The best-studied driver variant of *BRAF* occurs at codon 600 and is known as V600 (V600E, V600K); it is observed in approximately 50% of patients with melanoma, 25% with anaplastic thyroid cancer, and 2%–8% with non-small cell lung cancer.
  - (5) The use of combination BRAF and MEK inhibitors maximizes inhibition of the MAPK pathway and decreases the development of resistance compared to monotherapy with BRAF inhibitors (Subbiah et al., 2020).
  - (6) Examples of BRAF inhibitors include dabrafenib (oral), vemurafenib (oral), and encorafenib (oral). Examples of MEK inhibitors include cobimetinib (oral), trametinib (oral), and binimetinib (oral).
- d) B-cell receptor pathway inhibitors
- (1) Signaling mediated by B-cell receptors has a key role in the proliferation of B-cell neoplasms.
  - (2) Stimulation of the B-cell receptor leads to activation of spleen tyrosine kinase (SYK) and Lyn kinase, which activates Bruton tyrosine kinase (BTK) and phosphatidylinositol 3-kinase (PI3K).
  - (3) Inhibiting these pathways in B-cell malignancies leads to decreased cell proliferation (Crisci et al., 2019).
  - (4) Examples of BTK inhibitors include zanubrutinib (oral), acalabrutinib (oral), and ibrutinib (oral). Examples of PI3K inhibitors include idelalisib (oral), copanlisib (IV), duvelisib (oral), and umbralisib (oral).
- e) Cyclin-dependent kinase (CDK) inhibitors
- (1) CDKs are regulatory enzymes that control cell cycle transitions and eventual cell division.
  - (2) The transition from G<sub>1</sub> to S phase is controlled by the retinoblastoma protein through binding to *E2F* transcription factors, which halts the cycle cell at this stage. Inactivation of retinoblastoma leads to cell cycle progression.
  - (3) The binding of cyclin D to either CDK4 or CDK6 results in phosphorylation of retinoblastoma protein, release of *E2F* transcription factors, and cell cycle progression.
  - (4) Inhibition of CDK4/6 causes cell cycle arrest in the G<sub>1</sub> phase, leading to decreased cell viability.
  - (5) Estrogen has been shown to increase the rate of progression from the G<sub>1</sub> to S phase; therefore, targeting the CDK4/6 and retinoblastoma protein interaction is beneficial in estrogen receptor–positive breast cancer (Spring et al., 2019).
  - (6) Examples include abemaciclib (oral), palbociclib (oral), and ribociclib (oral).
- f) EGFR inhibitors
- (1) EGFR, a group of four related receptor tyrosine kinases, acts as a key mediator in cell signaling pathways, such as RAS/RAF/MEK, STAT, and PI3K/Akt/mTOR. It promotes cell proliferation, inhibition of apoptosis, angiogenesis, and metastatic spread.
  - (2) Overexpression of EGFR has been associated with many tumors, such as head and neck, breast, lung, colorectal, prostate, kidney, pancreatic, ovarian, and brain cancers.

**FIGURE 8-2.** Epidermal Growth Factor Receptor and Vascular Endothelial Growth Factor Receptor Pathways

Examples of targeted pathways. In these pathways, the extracellular receptor is activated, leading to a cascade of events resulting in enhanced gene expression, cell proliferation, cell survival, and migration.

EGFR—epidermal growth factor receptor; VEGFR—vascular endothelial growth factor receptor

Note. From "Growth Factor Receptors and Apoptosis Regulators: Signaling Pathways, Prognosis, Chemosensitivity and Treatment Outcomes of Breast Cancer," by S. Sarkar and M. Mandal, 2009, *Breast Cancer: Basic and Clinical Research*, 3, p. 52 (<https://doi.org/10.4137/bcbcr.s2492>). Licensed under Creative Commons Attribution 4.0 International License (CC-BY 4.0) (<https://creativecommons.org/licenses/by/4.0>).

- (3) Small molecule EGFR TKIs reversibly compete with adenosine triphosphate (ATP) for binding to the intracellular kinase domain, subsequently inhibiting EGFR autophosphorylation and downstream signaling.
  - (4) EGFR T790M variants lead to tumor resistance against first- and second-generation EGFR TKIs but can be targeted using third-generation TKIs (Ayati et al., 2020).
  - (5) Examples include afatinib (oral), erlotinib (oral), gefitinib (oral), and osimertinib (oral).
- g) Epigenetic mechanisms
- (1) Epigenetics is the study of heritable gene expression changes without changes to the nucleotide sequence of genes.
    - (a) This process is regulated by a variety of chemical-modifying enzymes and recognition proteins, including DNA methyltransferases, histone acetyltransferases, histone deacetylases (HDACs), methyl-binding domain proteins, and others (Zhong et al., 2021).
  - (2) HDAC inhibitors
    - (a) HDACs are epigenetic regulators that remove acetyl groups from the N-acetylated lysine residues of histones and nonhistone substrates.
  - (b) Epigenetic variants in cancer cells modify the structure and stability of the genome to initiate tumor growth and propagate carcinogenesis (Furtado et al., 2019). Available agents of epigenetic targets include HDAC inhibitors, enhancer of zeste homolog 2 (EZH2) inhibitors, and isocitrate dehydrogenase (IDH) inhibitors (Zhong et al., 2021).

- (b) Upregulation of HDAC has been observed in several malignancies, such as T-cell lymphoma and multiple myeloma, and causes alteration of oncogene and tumor suppressor gene transcription.
- (c) Inhibition of HDAC enables histone acetylation to increase by blocking the catalytic sites of HDACs, leading to growth arrest and apoptosis (Furtado et al., 2019).
- (d) Examples include belinostat (oral), panobinostat (oral), romidepsin (parenteral), and vorinostat (oral).
- (3) EZH2 inhibitors
  - (a) EZH2 is a member of a family of polycomb group genes, an important epigenetic regulator that represses transcription.
  - (b) EZH2 regulates cell cycle progression, autophagy, apoptosis, and cell senescence.
  - (c) It is also critical for promoting DNA damage repair.
  - (d) Alterations or abnormal expression of EZH2 may result in cancer initiation, progression, metastasis, metabolism, and drug resistance (Duan et al., 2020).
  - (e) An example is tazemetostat (oral).
- (4) IDH inhibitors
  - (a) The IDH family of enzymes consists of three isoforms (IDH1–IDH3) involved in many important cellular processes, including mitochondrial oxidative phosphorylation, glutamine metabolism, lipogenesis, glucose sensing, and regulation of cellular redox status (Idbaih & Touat, 2016).
  - (b) IDH1 and IDH2 driver variants are found in 20% of acute myeloid leukemia cases and occur more frequently in older individuals.
  - (c) These variants lead to the conversion of alpha-ketoglutarate into an oncogenic metabolite, R-2-hydroxyglutarate (R2HG), which accumulates, causes extensive epigenetic changes, and ultimately impairs cellular differentiation.
  - (d) IDH inhibitors block the activity of variant IDH to lower levels of R2HG, which induces blast differentiation (Alfayez & DiNardo, 2019).
  - (e) Examples include ivosidenib (oral IDH1 inhibitor) and enasidenib (oral IDH2 inhibitor).
- h) Exportin 1 (XPO1) inhibitors
  - (1) Proper cellular function requires the transport of larger molecules (including RNAs and proteins) between the nucleus and cytoplasm by transport receptors.
  - (2) XPO1 is a major transport receptor responsible for transporting multiple RNA species and proteins, including tumor suppressors (p53, BRCA1, BRCA2, and p27) and oncoproteins from the nucleus to the cytoplasm.
  - (3) The mechanism of action of XPO1 inhibitors has not been fully elucidated; however, it is postulated that it involves nuclear export blockade of tumor suppressor proteins (Azizian & Li, 2020).
  - (4) An example is selinexor (oral).
- i) Fibroblast growth factor receptor (FGFR) inhibitors
  - (1) FGFRs are expressed on cell surface membranes and consist of four isoforms (FGFR1–FGFR4).
  - (2) Binding fibroblast growth factors to these receptors promotes embryogenesis, angiogenesis, and tissue regeneration.
  - (3) Alterations of this process, through FGFR genetic substitutions, insertions, deletions, duplications, or fusions, lead to constitutive activation of the receptor through ligand-independent activation, which promotes the oncogenic process.
  - (4) FGFR alterations have been found in various solid tumor malignancies, including urothelial carcinoma, cholangiocarcinoma, endometrial cancer, ovarian cancer, breast cancer, non-small cell lung cancer, head and neck cancer, and glioblastomas (Weaver & Bossaer, 2021).
  - (5) Examples include erdafitinib (oral) and pemigatinib (oral).
- j) FMS-like tyrosine kinase 3 (FLT3) inhibitors
  - (1) FLT3 is a receptor tyrosine kinase expressed typically by hematopoietic stem or progenitor cells. It plays a key role in early-stage myeloid and lymphoid lineage development.
  - (2) Cell proliferation, survival, and differentiation are promoted by the binding of an extracellular ligand and activation of FLT3 signaling pathways, including PI3K, RAS, and STAT5.
  - (3) Alterations in FLT3 occur in approximately 30% of new diagnoses of acute myeloid

leukemia as internal tandem duplications or point variants in the tyrosine kinase domain.

- (4) Both variants lead to constitutive activation of the FLT3 kinase, resulting in proliferation and survival of acute myeloid leukemia (Daver et al., 2019).
  - (5) Examples include midostaurin (oral) and gilteritinib (oral).
- k) Hedgehog pathway inhibitors
- (1) The Hedgehog pathway is critical for embryonic development and tissue regeneration.
  - (2) Activation of the Hedgehog pathway causes the release of ligands that bind and suppress the transmembrane receptor Patched-1. Patched-1 is internalized from the cell membrane and degraded, resulting in the release of a transmembrane transducer known as Smoothened.
  - (3) Active Smoothened ultimately promotes the expression of target genes related to cell proliferation, survival, and differentiation.
  - (4) Abnormal signaling of the Hedgehog pathway can be caused by various mechanisms, including Hedgehog ligand upregulation and Patched-1 and Smoothened variants.
  - (5) The Hedgehog pathway has become a target for cancer therapies because of its close association with oncogenesis and the progression of cancers, including basal cell carcinoma and acute myeloid leukemia (Zhong et al., 2021).
  - (6) Examples include sonidegib (oral), vismodegib (oral), and glasdegib (oral).
- l) Human epidermal growth factor receptor (HER) 2 inhibitors
- (1) HER2, an oncoprotein situated on the long arm of chromosome 17, is part of the EGFR family, which includes EGFR (also known as HER1), HER2, HER3, and HER4.
  - (2) These receptors control cell growth, survival, differentiation, and migration.
  - (3) Overexpression and amplification of these receptors occur in 20%–25% of patients with breast cancer and may also occur in other cancers, such as gastric, lung, and colorectal. This results in dysregulated signaling through the PI3K and MAPK signaling pathways, leading to cell cycle progression and proliferation (Schlam & Swain, 2021).

- (4) Examples include lapatinib (oral), neratinib (oral), and tucatinib (oral).

m) Janus kinase (JAK) inhibitors

- (1) The JAK/STAT signaling pathway regulates many key cellular processes, including innate and adaptive immune responses, cell proliferation, differentiation, and apoptosis.
- (2) Binding of a ligand to transmembrane receptors initiates signaling of this pathway through activation of JAKs, subsequently leading to recruitment of specific signal transducer and activator of transcription (STAT) proteins.
- (3) STATs are phosphorylated by JAKs, resulting in translocation of STATs to the nucleus via importins, which bind to DNA and activate the transcription of target genes.
- (4) Abnormal signaling of the JAK/STAT pathway is primarily caused by variations and polymorphisms in JAK and STAT genes observed in the pathogenesis of several cancers (e.g., myeloproliferative neoplasms, leukemia) and other diseases (e.g., inflammatory skin conditions, autoimmune disorders).
- (5) JAK inhibitors suppress the enzymatic activity of JAK family members, inhibiting this signaling pathway (Moura & Fonseca, 2021).
- (6) Examples include ruxolitinib (oral), fedratinib (oral), and tofacitinib (oral).

n) Kirsten rat sarcoma viral oncogene homolog (KRAS) inhibitors

- (1) *KRAS* is the most frequently altered oncogene in human cancers.
- (2) It encodes for guanosine triphosphatase (GTPase), alternating between active and inactive states to regulate signal transduction.
- (3) These driver variants are typically associated with resistance to targeted therapies and poor treatment outcomes.
- (4) The *KRAS* p.G12C variant occurs in approximately 13% of patients with non-small cell lung cancer and 1%–3% of other solid tumors.
- (5) This oncoprotein enhances the proliferation and survival of tumor cells (Hong et al., 2020).
- (6) An example is sotorasib (oral).

o) Mammalian target of rapamycin (mTOR) kinase inhibitors

- (1) As a dual-specificity protein kinase, mTOR phosphorylates serine/threonine and tyro-

- sine residues to regulate cell growth, survival, metabolism, and immunity.
- (2) It activates multiple targets, such as ribosomal protein S6 kinase B-1, eukaryotic translation initiation factor 4E-binding protein 1, Akt, protein kinase C, and type-1 insulin-like growth factor.
  - (3) Deregulated mTOR activity is associated with various malignancies, including breast, prostate, lung, liver, and renal carcinomas.
  - (4) Upregulation of this signaling contributes to tumor growth and progression by promoting growth factor receptor signaling, angiogenesis, glycolytic metabolism, lipid metabolism, cancer cell migration, and suppression of autophagy.
  - (5) Several mTOR inhibitors with various mechanisms of action have been developed to combat this aberrant pathway (Hua et al., 2019).
  - (6) Examples include everolimus (oral) and temsirolimus (parenteral).
- p) Mediators of apoptosis B-cell lymphoma 2 (BCL2) inhibitors (BH3-mimetics)
- (1) Overexpression of BCL2 protein functions to protect cells from apoptosis through direct binding of the two main cell death effector proteins, BAX and BAK. BCL2 and other prosurvival proteins are naturally antagonized by the proapoptotic BH3-only protein subfamily.
  - (2) The balance of activity between prosurvival proteins and BH3-only proapoptotic proteins determines whether a cell will survive or undergo apoptosis.
  - (3) Malignant cells with upregulated BCL2 are protected from apoptosis despite cellular stresses.
  - (4) BH3-mimetics bind to a prosurvival protein such as BCL2 and inhibit the ability of BCL2 to bind to BAX or BAK, which allows permeability of the mitochondria, release of cytochrome C, and caspase activation, which all lead to apoptosis (Roberts, 2020).
  - (5) Examples include venetoclax (oral).
- q) Mesenchymal-epithelial transition factor (MET) inhibitors
- (1) *MET* is an oncogene encoding a tyrosine kinase receptor involved with embryogenesis, tumor growth, and metastasis.
  - (2) The dysregulation of the MET/hepatocyte growth factor (HGF) pathway is found in various solid tumor malignancies, including non-small cell lung, breast, cervical, stomach, and colon cancers. It is often associated with a poor prognosis (Liang & Wang, 2020).
  - (3) Examples include capmatinib (oral) and tepotinib (oral).
- r) Neurotrophin tyrosine receptor kinase (NTRK) inhibitors
- (1) *NTRK* gene fusions encode for the neurotrophin receptors tropomyosin receptor tyrosine kinase (TRK) A, TRKB, and TRKC and are known oncogenic drivers in many adult and pediatric malignancies.
  - (2) Ligand-binding activation of these receptors activates multiple intracellular pathways, including MAPK, PI3K, and protein kinase C, which ultimately regulate the transcription of genes involved in the differentiation and survival of neurons.
  - (3) Treatment of tumors harboring *NTRK* fusion with a TRK inhibitor inhibits the MAPK, PI3K/Akt, protein kinase C and STAT3 pathways (Cocco et al., 2018).
  - (4) Examples include larotrectinib (oral) and entrectinib (oral).
- s) Poly(ADP-ribose) polymerase (PARP) inhibitors
- (1) The PARP family of proteins primarily functions to repair damaged DNA.
  - (2) In response to single-strand DNA break, PARP1 recruits proteins to repair the DNA.
  - (3) In the absence of PARP, these single-strand breaks progress to double-strand breaks, which may be poorly repaired, especially in tumors with germline or somatic pathogenic variants in *BRCA1* or *BRCA2*.
  - (4) The combination of a double-stranded break in a *BRCA1/BRCA2*-altered cell and PARP inhibition results in the cell's inability to repair the damaged DNA, leading to cell death.
  - (5) Cells with *BRCA1/BRCA2* pathogenic variants are inherently more susceptible to PARP inhibition than wild-type cells; however, patients with wild-type *BRCA1/BRCA2* have benefited from PARP inhibition in some clinical trials (Hennes et al., 2020).
  - (6) Examples include olaparib (oral), rucaparib (oral), niraparib (oral), and talazoparib (oral).
- t) Proteasome inhibitors
- (1) Proteasomes are necessary for healthy cellular functions and to degrade misfolded or altered proteins.



- (2) The ubiquitin/proteasome pathway regulates fundamental processes, including apoptosis, cell growth and proliferation, DNA repair, unfolded protein response, and immune response.
  - (3) It removes damaged and misfolded proteins by first targeting the protein for degradation through ubiquitination. The protein then passes through the 20S proteasome, where it is degraded into small oligopeptides.
  - (4) Proteasome inhibitors prevent the degradation of ubiquitinated proteins. By inhibiting the translocation of the misfolded proteins out of the endoplasmic reticulum, the cell is under stress leading to cell cycle arrest and subsequent apoptosis (Fricker, 2020).
  - (5) Examples include bortezomib (subcutaneous or IV), carfilzomib (IV), and ixazomib (oral).
- u) Rearranged during transfection (RET) kinase inhibitors
- (1) The *RET* proto-oncogene encodes for a transmembrane receptor tyrosine kinase that plays a role in healthy embryonic development.
  - (2) Fusions between sequences that encode the kinase domain result in constitutively active, ligand-independent signaling and oncogenesis.
  - (3) RET fusions are typically mutually exclusive from other cancer drivers and lead to the dependence of the tumor cell on the oncogenic kinase.
  - (4) These fusions have been identified in 1%–2% of patients with non-small cell lung cancer and are associated with a high risk of developing brain metastases (Drilon et al., 2020).
  - (5) Examples include selpercatinib (oral) and pralsetinib (oral).
- v) ROS proto-oncogene 1 (ROS1) inhibitors
- (1) *ROS1* is a proto-oncogene related to the ALK, leukocyte receptor tyrosine kinase, and insulin receptor families.
  - (2) Rearrangements in *ROS1* are estimated to occur in 1%–2% of non-small cell lung cancers.
  - (3) Fusion of the ROS1 kinase with a partner leads to constitutive activation of the ROS1 kinase domain and phosphorylation and activation of downstream signaling through the MAPK/ERK, STAT3, and Akt pathways.
  - (4) Inhibition of ROS1 has been shown to decrease phosphorylation of these signals.
  - (5) Targeted agents against ALK fusions often also inhibit ROS1 due to the structural similarity of the kinase domains of the ROS1 and ALK proteins (Giustini & Bazhenova, 2020).
  - (6) Examples include crizotinib (oral), ceritinib (oral), cabozantinib (oral), entrectinib (oral), and lorlatinib (oral).
- w) Thrombopoietin (TPO) receptor agonists
- (1) TPO is the key cytokine that stimulates platelet production.
  - (2) TPO agonists bind to the TPO receptor, leading to conformational changes and JAK2/STAT5 pathway activation.
  - (3) Activation of this pathway increases megakaryocyte progenitor proliferation and platelet production.
  - (4) Available agonists in this class share the same mechanism of action; however, romiplostim is a peptibody that binds directly and competitively at the TPO binding site, whereas eltrombopag, a small molecule, binds at a transmembrane site.
  - (5) Examples include romiplostim (IV) and eltrombopag (oral).
- x) VEGF inhibitors
- (1) The VEGF pathway is an essential component of angiogenesis, the recruitment of new blood vessels to a tumor as it grows.
  - (2) This process is initiated by binding VEGF to receptors on the surface of endothelial cells.
  - (3) Angiogenesis holds an important role in cancer progression through generating new blood vessels to supply tumors with oxygen and nutrients necessary for growth and metastases.
  - (4) Angiogenesis inhibitors interfere with this process by binding to VEGF and its receptor or other proteins in the downstream signaling pathway to block activation of this pathway (National Cancer Institute, 2018).
  - (5) Examples include axitinib (oral), lenvatinib (oral), pazopanib (oral), sorafenib (oral), sunitinib (oral), and ziv-aflibercept (IV).
- y) Multiple kinase targets
- (1) These agents target multiple kinase pathways, leading to alterations in cell proliferation. The exact primary target is unknown.
  - (2) Examples include cabozantinib (oral) and regorafenib (oral).

### B. Adverse effects of targeted therapies

1. In contrast to cytotoxic agents, targeted therapies interfere with specific pathways in cancer cells, with little or no effect on healthy tissues. Consequently, they have a nontraditional side effect profile compared to cytotoxic agents (National Cancer Institute, 2018).
2. Table 8-1 and Figure 8-3 include notable side effects for the different targeted agents. These include acneiform rash, diarrhea, cardiotoxicity, hepatotoxicity, hypertension, metabolic abnormalities (e.g., hyperglycemia, hyperlipidemia), and others.

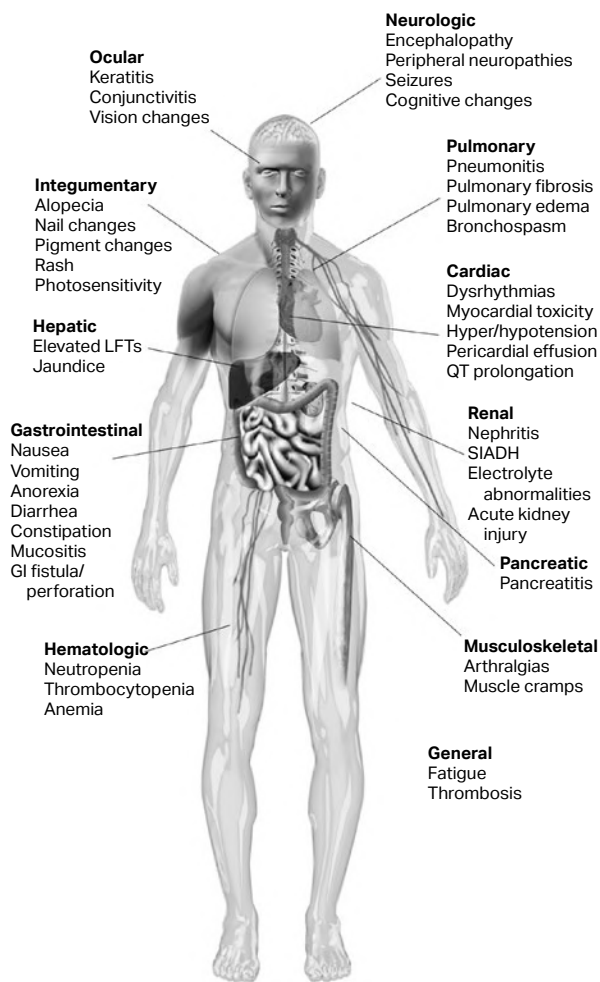
### C. Drug–drug interactions

1. Cytochrome P450 (CYP) enzymes are expressed primarily in the liver and are responsible for the metab-

olism of drugs. Although more than 50 of these enzymes exist, six metabolize most drugs—CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5.

2. Drugs can inhibit or induce these enzymes, leading to drug–drug interactions. The clinical outcome of these interactions can be adverse reactions or therapy failures from overexposure or underexposure to the intended medication. For example, ritonavir is a strong inhibitor of CYP3A4. Many TKIs are metabolized by CYP3A4; therefore, coadministration with ritonavir or another strong inhibitor may decrease TKI metabolism and increase toxicity. Inducers of CYP3A4, such as rifampin, carbamazepine, and St. John's wort, can increase TKI metabolism and decrease efficacy (Rimassa et al., 2019).
3. Many TKIs undergo metabolism via CYP pathways, leading to a high propensity for drug–drug interactions. Table 8-1 includes specifics to avoid interactions.

**FIGURE 8-3.** Potential Side Effects and Toxicities of Targeted Therapy by System



GI—gastrointestinal; LFTs—liver function tests; SIADH—syndrome of inappropriate antidiuretic hormone secretion

Note. Image courtesy of University of Texas MD Anderson Cancer Center. Used with permission.

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## CHAPTER 9

# Principles of the Immune System

### A. Overview of immunology

1. Current advances in immunotherapy use immune pathways and cellular mechanisms as a therapeutic approach to the treatment and prevention of cancer. Basic knowledge of the immune system and immune response to tumor cells is essential to understanding the clinical application of immunotherapy.
2. The immune system is a highly specialized and adaptive system of barriers, organs, cells, and molecules that guard an individual by providing the following (Abbas et al., 2019; see Figure 9-1):
  - a) Protection: defense against foreign pathogens (i.e., bacteria, viruses, fungi, and parasites)
  - b) Homeostasis: elimination of damaged or dead cells and initiation of tissue repair
  - c) Surveillance: identification of foreign or nonself substances; inhibition of tumor growth

### B. Types of immune response (see Figure 9-2)

1. An immune response is the reaction of the immune system against a foreign substance or antigen (e.g., bacteria).
2. The immune system consists of two types of immunity: innate and adaptive (Abbas et al., 2019; see Table 9-1).
  - a) Innate immunity (natural or native immunity)
    - (1) Innate immunity is the first line of defense and is essential for inducing a nonspecific response to a pathogen or foreign substance (Sompayrac, 2019). It does not generate immunologic memory.
    - (2) Components of innate immunity (Frizinsky et al., 2019)
      - (a) Physical barriers (e.g., skin, mucous membranes)
      - (b) Mechanical barriers (e.g., coughing, sneezing, blinking)
      - (c) Chemical barriers (e.g., tears, acidic pH, sweat)
      - (d) Inflammatory barriers (e.g., vascular fluid leakage)

- (e) Complement activation (e.g., plasma proteins mark pathogens for destruction)
- (f) Acute-phase protein production (e.g., recruiting phagocytes to the site of infection or tissue injury)
- (g) Large granular lymphocyte production (e.g., kill and digest pathogens)

### b) Adaptive or acquired immunity

**FIGURE 9-1.** Primary and Secondary Lymphoid Organs

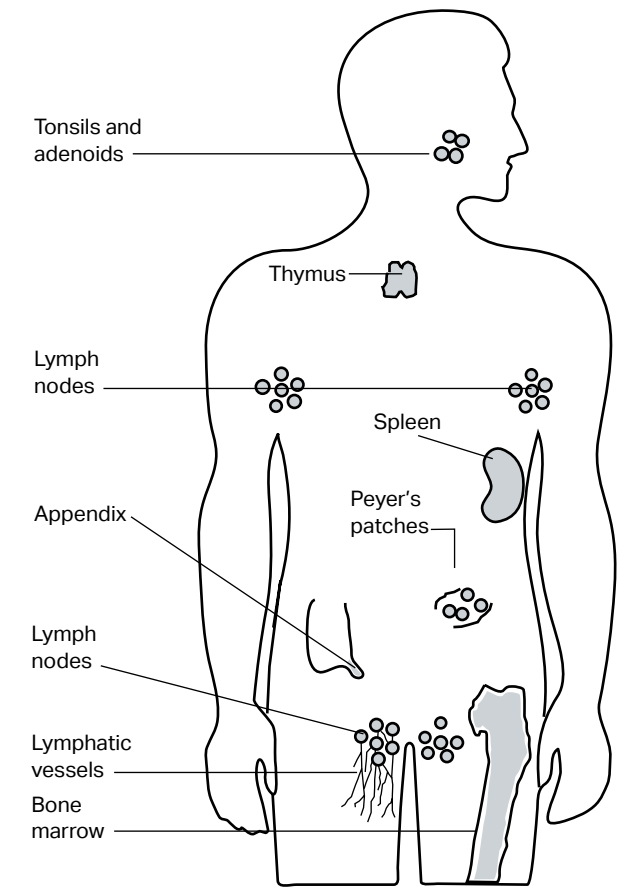
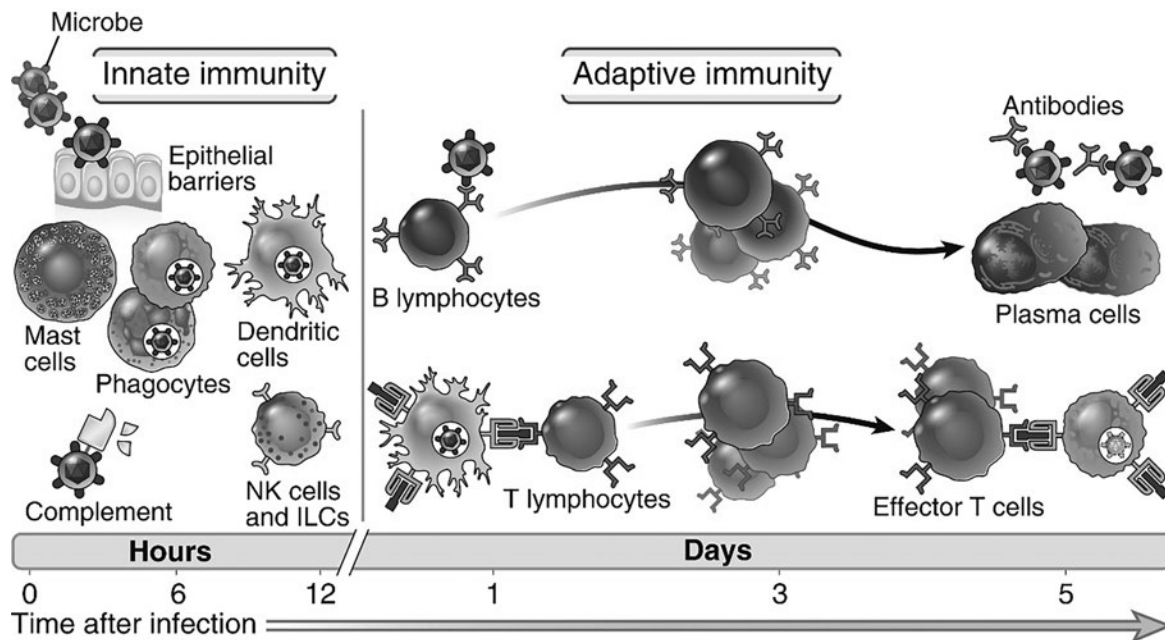


**FIGURE 9-2.** The Innate and Adaptive Immune Response

The innate immune response functions as the first line of defense against infection. It consists of soluble factors, such as complement proteins, and diverse cellular components including granulocytes (basophils, eosinophils and neutrophils), mast cells, macrophages, dendritic cells, natural killer (NK) cells, and innate lymphoid cells (ILCs). The adaptive immune response is slower to develop but manifests as increased antigenic specificity and memory. It consists of antibodies, B cells, T lymphocytes, and effector T cells.

Note. From *Basic Immunology: Functions and Disorders of the Immune System* (6th ed., p. 20), by A.K. Abbas, A.H. Lichtman, and S. Pillai, 2019, Elsevier. Copyright 2019 by Elsevier. Reprinted with permission.

- (1) Adaptive immunity is often considered the second line of defense and involves immunologic memory, specificity, and collaboration of B and T cells (Medina, 2016).
- (2) Three types of adaptive immunity
  - (a) Humoral immunity is mediated by B cells and plasma cells, resulting in the production of immunoglobulins (Igs) or antibodies (Sompayrac, 2019).
  - (b) Cell-mediated immunity is mediated primarily by T cells and cytokine products. The cytotoxic T cells and helper T cells (type 1 or 2) react to self-antigens or a foreign pathogen through T-cell receptor signaling (Butcher & Zhu, 2021; Sompayrac, 2019; Wu et al., 2020).
  - (c) Regulatory T cells, formerly known as suppressor T cells, limit the activity of other immune effector cells (Zhao et al., 2017).
- i. Their primary role is to prevent the onset of immunity to healthy tissue (autoimmune disease) and limit the inflammatory response that can occur with infections.
- ii. Absence of regulatory T cells may trigger inflammatory disorders primarily involving the bowel, skin, and liver.
- C. Organs of the immune system (Abbas et al., 2019; Ruddle, 2020; Thapa & Farber, 2019)
  1. The immune system consists of primary and second (peripheral) lymphoid organs.
  2. Primary lymphoid organs are bone marrow and thymus. They are sites of lymphocyte development and differentiation.
  3. Second (peripheral) lymphoid organs include lymph nodes, spleen, Peyer patches, adenoids, tonsils, and mucosa-associated lymphoid tissue. They are sites of antigen-driven proliferation and lymphocyte maturation.

**TABLE 9-1.** Adaptive and Innate Immune Responses

| Immune Response | Mechanism of Action                                 | Cells Primarily Involved                                                                                        |
|-----------------|-----------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|
| Innate          | Primary line of defense<br>Nonspecific<br>No memory | Neutrophils<br>Monocytes<br>Macrophages<br>Dendritic cells<br>Large granular lymphocytes (natural killer cells) |
| Adaptive        | Secondary line of defense<br>Specific memory        | B lymphocytes (in humoral immunity)<br>T lymphocytes (in cell-mediated immunity)                                |

Note. Based on information from Abbas et al., 2019.

#### D. Cells of the immune system (see Figure 9-3)

1. The immune response involves the intricate interaction of several cells and proteins. Cells are widely categorized by their progenitor bone marrow cell lines (Sompayrac, 2019).
2. Myeloid cells arise from the myeloid stem cell line, giving rise to red blood cells and platelets (Weiskopf et al., 2016).
  - a) Myeloid cells involved in the immune system include monocytes, macrophages, dendritic cells, granulocytes, and mast cells.
  - b) Granulocytes are composed of four subsets: neutrophils, eosinophils, basophils, and mast cells. Neutrophils are the first responders, phagocytosing infection and initiating inflammation.
3. Lymphocytes arise from the lymphoid stem cell line and include effector cells, which are short-lived naïve cells activated during an immune response.
  - a) Effector cells include T cells (cytotoxic T cells and helper T cells), which produce cytotoxic molecules, and B cells (plasma cells), which produce antibodies that function to eliminate antigens (Abbas et al., 2019).
    - (1) T cells
      - (a) Helper T cells coordinate the immune response and cell-mediated immunity; they are required to maintain cytotoxic T-cell responses and express cluster of differentiation (CD) 4, which assists in stimulating macrophages, B cells, and CD8-positive T-cell production.
        - i. Type 1 helper T cells are necessary for activating macrophages and are involved in producing specific antibody isotypes.

- ii. Type 2 helper T cells are effective activators of B cells, particularly in primary responses.

(b) Cytotoxic T cells kill foreign cells, virally infected cells, or cells with new surface antigens.

- i. Cytotoxic T cells express CD8.
- ii. T cells secrete cytokines such as tumor necrosis factor and interferon gamma.
- iii. Additionally, CD8 functions as a co-receptor for T-cell receptors and T-cell signaling, regulating cell proliferation, differentiation, survival, and cytokine production.

(c) Regulatory T cells

- i. These cells interfere with the development of an immune reaction when recognizing an antigen.
- ii. Their primary role is to modulate the severity of inflammation produced by infection and prevent autoimmunity; they may be involved in malignancy.

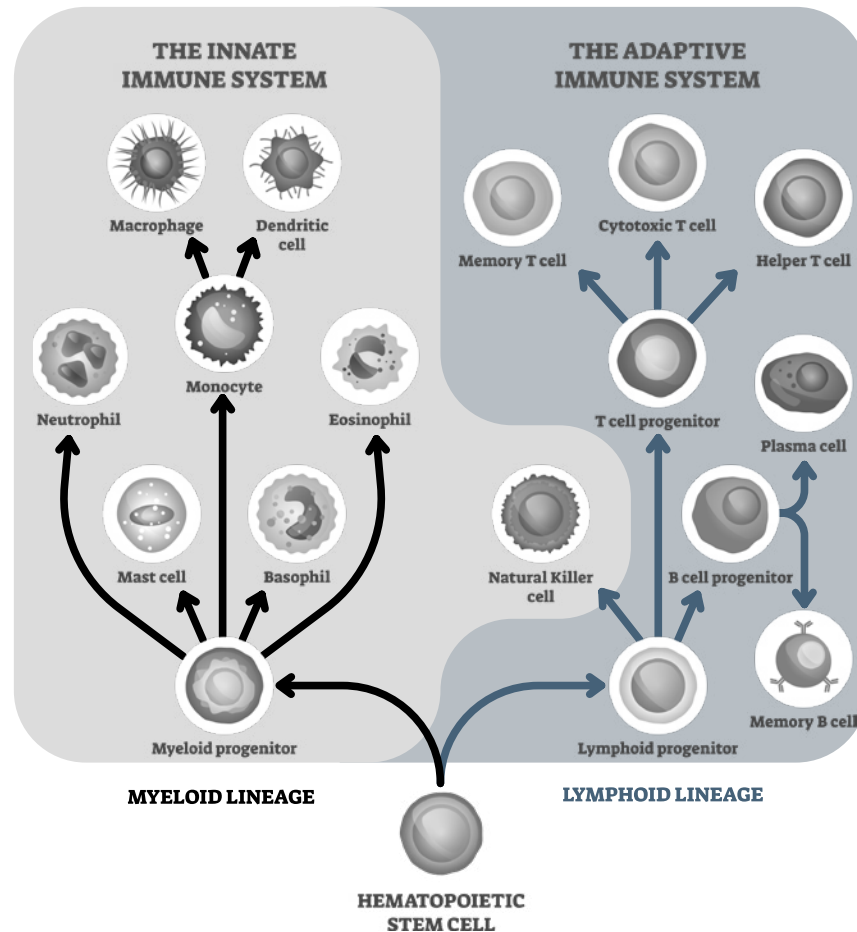
(d) Memory T cells recognize specific antigens and induce recall responses.

(2) B cells involved in mediated immunologic memory give rise to plasma cells and memory B cells (Sompayrac, 2019).

(a) Plasma cells manufacture antibody molecules specific to a target antigen.

- i. The function of the plasma cell is to enhance effector cell functions. Most peripheral blood antibodies are IgG, which enhances the phagocytosis of antigens by macrophages, monocytes, polymorphonuclear cells, and some lymphocytes.
- ii. IgM is the first antibody produced in response to an antigen.
- iii. IgA is present in body secretions and helps prevent infections at sites where the environment interacts with the body, such as the nose and lungs.
- iv. IgD is present in small amounts in normal serum. The exact biologic function is unclear; however, IgD may have some antibody function for penicillin, diphtheria, and insulin.



**FIGURE 9-3.** Cells of the Immune System

Note. Image courtesy of iStock. Used with permission.

v. IgE exists in trace amounts in normal serum and is associated with immediate hypersensitivity reactions. IgE antibodies are generated when combined with specific antigens, thus activating histamine release from mast cells.

(b) Memory B cells recognize a specific antigen and can survive for an extended period after clearance of the primary infestation. They can quickly produce antigen-specific antibodies upon re-exposure (Abbas et al., 2019).

b) Natural killer (NK) cells

(1) NK cells are effector lymphocytes of the innate immune system. They are important because of their ability to induce cell death in tumor cells and virally infected

autologous cells by producing substances that can bind to and destroy foreign invaders without identifying a specific antigen.

(2) NK cells identify foreign substances by their lack of identifying surface molecules (Abel et al., 2018).

c) NK T cells have both NK and T-cell markers and produce cytokines without differentiating into effector cells or having prior sensitization (Abel et al., 2018).

#### E. Immune system proteins and receptors

1. Cells of the immune system evaluate structures (antigens) on membranes of circulating cells as a critical step in immune response (Actor, 2019; Gonzalez et al., 2018; Jhunjhunwala et al., 2021).
2. Receptor tyrosine kinases (RTKs) are membrane-bound molecules that, when stimulated, send intracellular signals to the DNA, culminating in cell proliferation and migration (Keith & Abueg, 2015).



- a) RTKs can often be variated or overexpressed in malignant tumors. RTK variants may result in changes in cellular pathways that affect intracellular signal activation in the absence of the appropriate extracellular growth signal, resulting in unregulated tumor growth.
  - b) The epidermal growth factor receptor family (EGFR1, EGFR2, EGFR3, and EGFR4) of RTKs is widely distributed in healthy tissue. EGFR is a known driver of carcinogenesis in breast cancer, lung cancer, melanoma, glioblastoma, and gastrointestinal tumors.
  - c) Other major RTKs implicated in oncogenesis include platelet-derived growth factor receptor (PDGFR), ROS oncogene 1 (ROS1), anaplastic lymphoma kinase (ALK), and mesenchymal-epithelial transition factor (MET).
3. CD markers are surface-bound proteins that act as receptors and ligands to neighboring cells (Shahrabi et al., 2020).
- a) Diagnostic immunophenotyping assays use CD antigens to sort, identify, and measure cells based on the molecules present on the cell surface.
  - b) The CD nomenclature and numbering system is a standardized protocol used to identify these molecules (see Table 9-2).
4. RTKs and CDs are common targets of immunotherapy.
- a) Some monoclonal antibodies target the surface-bound RTKs, inducing immune-mediated cellular toxicity and halting cell signal transduction.
  - b) Small molecule tyrosine kinase inhibitors disrupt the interaction between molecules of the cell signal transduction pathways.
5. Inhibitory and regulatory proteins limit autoimmunity.
- a) Autoimmunity occurs when the immune system mounts anti-self B-cell and T-cell reactions after mistaking healthy self-tissues as foreign (National Cancer Institute, n.d.).
  - b) Regulatory T cells suppress exaggerated immune responses and reactions to self-molecules (Rocamora-Reverte et al., 2021).
  - c) Immune checkpoint molecules inhibit T-cell responses, protecting the host from self-attack (Ohue & Nishikawa, 2019; Seidel et al., 2018; Zhang et al., 2018).
    - (1) Cytotoxic T-lymphocyte antigen 4 (CTLA-4) ligands bind to antigen-presenting cells, downregulating T-cell activity.
      - (a) CTLA-4 expression decreases the activation of T cells and sends inhibitory signals to the T cell.
      - (b) CTLA-4 is expressed by activated CD8-positive cells, but the primary

**TABLE 9-2.** Cluster of Differentiation Cell Expression

| Cluster of Differentiation Cell | Normal Expression                                                                                  | Increased Expression                                       |
|---------------------------------|----------------------------------------------------------------------------------------------------|------------------------------------------------------------|
| CD3                             | T-cell receptors                                                                                   | Leukemia<br>T-cell lymphoma                                |
| CD19                            | B cells<br>Dendritic cells<br>Stem cells                                                           | B-cell malignancies                                        |
| CD20                            | B cells<br>T cells                                                                                 | Non-Hodgkin lymphoma                                       |
| CD22                            | B cells<br>Stem cells                                                                              | B-cell malignancies                                        |
| CD25                            | Regulatory T cells                                                                                 | Non-Hodgkin lymphoma                                       |
| CD30                            | B cells<br>Endothelial cells<br>Macrophages<br>NK cells<br>Stem cells<br>T cells                   | B-cell malignancies<br>Hodgkin lymphoma<br>T-cell lymphoma |
| CD33                            | Dendritic cells<br>Granulocytes<br>Macrophages<br>Stem cells                                       | Acute myeloid leukemia                                     |
| CD34                            | Stem cells                                                                                         | Blast marker in acute myeloid leukemia                     |
| CD38                            | B cells<br>Dendritic cells<br>Macrophages<br>NK cells<br>Stem cells<br>T cells                     | Leukemia<br>Multiple myeloma                               |
| CD44                            | B cells<br>Endothelial cells<br>Erythrocytes<br>Granulocytes<br>Macrophages<br>NK cells<br>T cells | Acute myeloid leukemia                                     |
| CD53                            | B cells<br>Macrophages<br>NK cells<br>Stem cells<br>T cells                                        | B-cell malignancies                                        |
| CD185                           | B cells<br>Follicular helper T cells                                                               | Non-Hodgkin lymphoma                                       |
| CD117                           | Stem cells                                                                                         | Blast marker in acute myeloid leukemia                     |

CD—cluster of differentiation; NK—natural killer

Note. Based on information from National Cancer Institute, 2021; Shahrabi et al., 2020.

role of CTLA-4 is diminishing activity of helper T cells and enhancing the immunosuppressive activity of regulatory T cells (Rowshanravan et al., 2018).

- (2) Programmed cell death protein 1 (PD-1)
    - (a) PD-1 is a membrane-bound inhibitory receptor on T cells, B cells, and NK cells.
    - (b) PD-1 interaction with programmed cell death-ligand 1 (PD-L1) inhibits T-cell proliferation and cytotoxic function and induces T-cell regulatory function and apoptosis.
  - (3) Tumors may overexpress PD-L1, shielding them from an immune response. Diagnostic assays measure PD-L1 expression and have been used as a predictive biomarker for sensitivity to checkpoint inhibitor therapy in some cancers (Davis & Patel, 2019).
6. Immune cell communication is coordinated by cytokines.
- a) Cytokines
    - (1) Cytokines are glycoprotein products of immune cells, such as lymphocytes and macrophages.
    - (2) Cytokines are produced in response to T-cell activation and mediate effector defense functions.
    - (3) Cytokines coordinate an immune response that can be cytotoxic (e.g., interleukins, interferon) (Berraondo et al., 2019; Korbecki et al., 2020; Morein et al., 2020; Nagarsheth et al., 2017).
  - b) Chemokines, or chemotactic cytokines, are protein molecules that regulate leukocyte migration and are essential organizers of cell distribution in immune and inflammatory responses (Battle & Massagué, 2019; Berraondo et al., 2019; Korbecki et al., 2020; Wang et al., 2020).
  - c) In the tumor microenvironment, tumors manipulate cytokine and chemokine expression to suppress the immune response and promote tumor proliferation and migration.
  - d) Exogenous administration of chemokines and cytokines can be used in anticancer therapies.

#### F. Phases of immune response (Abbas et al., 2019; Sompayrac, 2019)

1. Antigen recognition: Circulating antibodies recognize a foreign antigen, which activates the immune system.
  - a) Antigens are molecular structures that are recognized by and can stimulate the immune system. Tumor antigens are either cell surface molecules

that function as targets for antibody responses or intracellular molecules presented within the context of major histocompatibility complex molecules capable of T-cell recognition (Jongsma et al., 2021).

- b) Antigen-presenting cells (e.g., macrophages, B cells, dendritic cells) efficiently present the antigen to T cells; only dendritic cells can initiate a primary immune response.
  - c) Antigen presentation must occur in the presence of inflammatory factors to generate an immune response. Antigen presentation in the absence of a noninflammatory environment can result in immune tolerance.
2. Lymphocyte activation: B or T cells are activated to proliferate and differentiate into effector lymphocytes.
  3. Effector phase: Foreign antigen is inactivated or destroyed.
  4. Contraction: During this phase, T-cell expansion is inhibited or activated cells are eliminated by apoptosis, facilitating the immune system's return to a resting state and limiting tissue damage and chronic inflammation.
  5. Memory: Lymphocytes that survive the immune response become memory cells that can recognize a former antigen and initiate a rapid response.

#### G. Tumor escape mechanisms

1. Immune surveillance refers to the process “whereby the immune system identifies cancerous and/or pre-cancerous cells and eliminates them before they can cause harm” (Swann & Smyth, 2007, p. 1137). Cancer cell formation occurs when immune surveillance fails (Swann & Smyth, 2007).
2. Theories of tumor escape mechanisms (Bates et al., 2018; Cornel et al., 2020; Friedrich et al., 2019; Mortezaee, 2020; Shembrey et al., 2019)
  - a) Tumors manipulate antigen presentation as a mechanism of tumor escape (altered immunogenicity). Alterations to antigen presentation weaken immune recognition and dampen immune response (Jhunjhunwala et al., 2021; Jongsma et al., 2021; Seliger, 2019).
    - (1) Tumors express surface antigens also expressed on self-cells, then evade the immune system.
    - (2) Neoantigens are products of acquired gene variants resulting in altered antigen expression on the tumor cell surface, allowing the antigen to go unrecognized by the humoral immune system (Zhang et al., 2021).
    - (3) Major histocompatibility complex molecule loss or alteration blunts cell-mediated

- immune response. The peptide epitope (antigen) that binds to the major histocompatibility complex molecule and is recognized by T cells is lost or mutated.
- (4) Antibodies produced as part of the immune response cause antigens to enter the tumor cell or leave it entirely. This further limits the immune cells' ability to recognize the tumor cell as nonself.
- b) Acquired deficiencies in immune sensitivity (Hong et al., 2019)
- (1) These include age- and disease-associated alterations, such as decreased or increased apoptosis and signaling defects of T cells.
  - (2) Immunologic aging or immunosenescence causes the following:
    - (a) Decreased number of naïve T cells; decreased generation of cytotoxic T cells, hematopoietic stem cells, phagocytes, and NK cells
    - (b) Decreased production of interleukin-2
    - (c) Decreased signal transduction of lymphocytes
    - (d) Decreased humoral immunity
    - (e) Decreased antigen response and proliferation, increased memory T cells, and a potentially decreased number of functional regulatory T cells
- c) Tumors develop adaptive mechanisms to evade immune detection (Baghban et al., 2020; Giraldo et al., 2019; Mortezaee, 2020).
- (1) Tumors hijack the expression of immune checkpoints (e.g., CTLA-4, PD-1, lymphocyte activation gene 3 [known as *LAG3*]), which inhibit usual T-cell activity.
  - (2) High levels of PD-L1 expression promote immune system tolerance and allow for unchecked tumor growth (Davis & Patel, 2019).
    - (a) Tumors fail to give off inflammatory warning signals to stimulate an immune response. T-cell interaction in the absence of inflammatory signals results in sustained immune tolerance.
    - (b) Tumors recruit regulatory T cells that suppress T-cell activity.
    - (c) The tumor itself produces substances that alter or inhibit the body's immune response. Examples include transforming growth factor-beta, interleukin-10, and adenosine, which limit T-cell toxicity functions.
  - d) Immunoediting is the development of an immune-resistant tumor mass resulting from a prior immune attack. Three phases lead to its development (Batlle & Massagué, 2019; O'Donnell et al., 2019; Swann & Smyth, 2007; Teng et al., 2013).
    - (1) In the elimination phase, cellular and humoral immune cells eliminate highly immunogenic tumor cells. Cells with low immunogenicity survive.
    - (2) Tumor cells with low immunogenicity are ignored by a tolerant immune system during the equilibrium phase.
    - (3) The tumor mass is allowed to grow and spread unchecked in the escape phase.
3. Angiogenesis (Al-Ostoot et al., 2021; Loizzi et al., 2017; Saman et al., 2020; Teleanu et al., 2020; Zuazo-Gaztelu & Casanovas, 2018)
- a) Angiogenesis is the development of new blood vessels. It is a complex, multistep process required for many healthy functions, including wound healing, tissue repair, reproduction, growth, and development.
- (1) Healthy angiogenesis occurs in response to physiologic demands, such as hypoxia, wound healing, growth, or acidosis.
  - (2) Healthy angiogenesis is tightly controlled by the balance of vascular mediators that ensure blood vessel growth is limited to physiologic needs.
  - (3) Vascular endothelial growth factor is expressed on endothelial cells and is an important mediator of angiogenesis.
  - (4) Other angiogenic mediators include hypoxia-inducible factor-1 angiopoietins, platelet-derived growth factor, fibroblast growth factor, granulocyte-colony-stimulating factor, interleukin-8, matrix metalloproteases, hepatocyte growth factor, tumor necrosis factor, transforming growth factor, epidermal growth factor, interferons (alpha, beta, and gamma), and endostatin.
- b) Tumor angiogenesis is the development of new blood vessels within a tumor (Loizzi et al., 2017; Lugano et al., 2020).
- (1) Angiogenic switch occurs when the balance of angiogenic mediators is disrupted, leading to tumor angiogenesis.
  - (2) Endothelial cells line the vasculature of healthy tissues. In a resting state, they provide a homeostatic barrier that prevents the uncontrolled extravasation of intravascular components and inhibits coagulation.

- (3) Tumors produce an overabundance of angiogenic factors that stimulate receptors on endothelial cells.
  - (4) Stimulated endothelial cells secrete enzymes (matrix metalloproteinases) that digest the basement membrane, stimulating the release of proangiogenic factors from neighboring endothelial cells.
  - (5) Stimulated endothelial cells then sprout new capillaries that grow toward the source of the proangiogenic factors (the tumor).
  - (6) Poorly formed, leaky tumor vasculature excretes proangiogenic factors that further stimulate the cycle of tumor vascular growth. Leaky tumor vasculature hampers the delivery of chemotherapy to the tumor site.
  - (7) Blood flow in tumors is sluggish, thus inducing hypoxia and acidosis, further triggering angiogenesis.
- c) Angiogenesis inhibitors (antiangiogenics) are therapeutic agents that block angiogenesis.

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## CHAPTER 10

# Immunotherapy

### A. Overview

1. *Immunotherapy* is a broad term that refers to many different therapies. It harnesses the body's immune system to eradicate cancer cells.
2. Multiple modalities exist in which immunotherapy is administered, including cytokines, vaccines, immune checkpoint inhibitors, oncologic viral therapies, monoclonal antibodies (e.g., radioimmunotherapy), and chimeric antigen receptor (CAR) T-cell therapy (Abbott & Ustoyev, 2019).

### B. Modalities of immunotherapy

#### 1. Immune checkpoint inhibitors

##### a) Pathophysiology

- (1) The immune system uses inhibitory and stimulatory pathways to regulate the cells and the immune response process to identify and eliminate abnormal cells. It has been found that some cancers disrupt these pathways and avoid recognition (Bayer et al., 2017).
- (2) Stimulation of select immune checkpoints blocks the proteins and receptors that help moderate immune response and prevent T lymphocytes from recognizing and killing cancer cells. Immune checkpoint inhibitors help block the stimulation of these regulatory signals that inhibit T cells, and T cells are released and can elicit an immune response against cancer cells.
- (3) Several immune checkpoint inhibitors have been approved for the treatment of cancer, including anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4), anti-programmed cell death protein 1 (PD-1), and anti-programmed cell death-ligand 1 (PD-L1) (Postow et al., 2018).
- (4) Currently, clinical trials are using several drugs that target other immune checkpoints.

##### b) Mechanism of action

- (1) CTLA-4 is a first-in-class target for immune checkpoint inhibitors. It is a receptor found on T cells and engaged by its ligand B7 to prevent overactivation. Blockade of CTLA-4 allows for continued T-cell activation, thus enhancing antitumor responses (Bayer et al., 2017). An example includes ipilimumab.
  - (2) PD-1 is an inhibitory pathway present on activated T cells. It binds to the PD-L1 and PD-L2 ligands. Stimulation of the PD-1 pathway leads to disruption of immune surveillance and antitumor response. Immune checkpoint inhibitors targeting PD-1 can disrupt this process, allowing for continued T-cell activation and tumor surveillance and elimination (Mahoney et al., 2015). Examples include nivolumab, pembrolizumab, cemiplimab, and dostarlimab.
  - (3) PD-L1 can be found on cancer cells. It has an affinity for binding to PD-1 and B7 receptors, which initiates a pathway that inhibits T-cell activation. Blocking PD-L1 can help restore immune activity (Chen et al., 2012; Mahoney et al., 2015). Examples include atezolizumab, avelumab, and durvalumab.
- c) Applications and indications: Since the introduction of immune checkpoint inhibitors in 2011, the U.S. Food and Drug Administration (FDA)-approved indications and clinical applications have markedly expanded and include solid tumor and hematologic malignancies. These agents are used as a single-agent therapy and combined with other anticancer therapies to treat a variety of cancers. As of the date of publication, indications by agent are presented in Table 10-1.
- d) Administration: Immune checkpoint inhibitors are administered via IV infusion.



**TABLE 10-1.** Immunotherapy Agents

| Classification          | Mechanism of Action                                                                                                                                                                                                                                                                                           | Drug                                                                          | Route | Indications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Side Effects                                                                                                                                                                                                                                                                                             | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|-------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|-------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Antibody-drug conjugate | Chimeric monoclonal antibody targeting CD30, attached to anti-microtubule agent MMAE; binds to CD30-expressing cells, resulting in internalization and intracellular cleaving of the conjugate, releasing MMAE, which disrupts the cellular microtubule network, resulting in cell cycle arrest and apoptosis | Brentuximab vedotin (anti-CD30 antibody; Adcetris <sup>®</sup> ) <sup>a</sup> | IV    | <p>Previously untreated stage III or IV cHL, in combination with chemotherapy</p> <p>cHL at high risk for relapse after autologous HSCT</p> <p>cHL after the failure of autologous HSCT or after the failure of at least 2 prior chemotherapy regimens</p> <p>Previously untreated CD30-expressing peripheral T-cell lymphoma, in combination with chemotherapy</p> <p>Systemic anaplastic large cell lymphoma after the failure of at least 1 prior chemotherapy regimen</p> <p>Primary cutaneous anaplastic large cell lymphoma or CD30-expressing mycosis fungoides in patients who have received prior systemic therapy</p> | Peripheral neuropathy, fatigue, rash, neutropenia, anemia, upper respiratory tract infection, cough, fever, infusion-related reactions, nausea, constipation, vomiting, alopecia, decreased weight, abdominal pain, stomatitis, thrombocytopenia, lymphopenia, mucositis, renal toxicity, hepatotoxicity | <p>Previously untreated stage III or IV cHL: Recommended dosage is 1.2 mg/kg IV (maximum 120 mg) over 30 minutes every 2 weeks until a maximum of 12 doses, disease progression, or unacceptable toxicity.</p> <p>Other indications: Recommended dosage is 1.8 mg/kg IV (maximum 180 mg) over 30 minutes every 3 weeks.</p> <p>Do not administer as an IV push or bolus.</p> <p>In patients who have experienced a prior infusion-related reaction, premedication may include acetaminophen, an antihistamine, and a corticosteroid.</p> <p>Reduce dose in patients with mild hepatic or renal impairment.</p> <p>Monitor liver enzymes and bilirubin.</p> <p>Monitor CBC prior to each dose. Monitor more frequently for patients with grade 3–4 neutropenia. Monitor patients for fever. If grade 3–4 neutropenia develops, consider dose delays, reductions, discontinuation, or G-CSF prophylaxis with subsequent doses.</p> <p>Advise patients to report symptoms of pulmonary toxicity, hepatotoxicity, and dermatologic toxicity.</p> <p>Store reconstituted vials or diluted solutions at 2°C–8°C and use within 24 hours.</p> <p>Monitor for TLS in patients with a rapidly proliferating tumor or high tumor burden.</p> <p>Start primary prophylaxis with G-CSF beginning with cycle 1 for patients who receive brentuximab vedotin in combination with chemotherapy for previously untreated stage III or IV cHL or previously untreated peripheral T-cell lymphoma.</p> <p>Serious infections and opportunistic infections have been observed. Monitor for bacterial, fungal, and viral infections.</p> <p>(Seagen, 2020)</p> |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                              | Mechanism of Action                                                                                                                                                                                                                                                                                                                 | Drug                               | Route | Indications                                                                                                                                                                                                         | Side Effects                                                                                                                                                                                                                                                                                                                                               | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|---------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|-------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Antibody-drug conjugate<br>( <i>Cont.</i> ) | Human monoclonal antibody targeting adhesion protein nectin-4, attached to anti-microtubule agent MMAE; binds to nectin-4-expressing cells, resulting in internalization and intracellular cleaving of the conjugate, releasing MMAE, which disrupts the cellular microtubule network, resulting in cell cycle arrest and apoptosis | Enfortumab vedotin-ejfv (Padcev®)  | IV    | Locally advanced or metastatic urothelial cancer in adults after treatment with a PD-1 or PD-L1 inhibitor and platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced, or metastatic setting | Fatigue, peripheral neuropathy, decreased appetite, rash, alopecia, nausea, dysgeusia, diarrhea, pruritus, dry skin<br>Ocular disorders: dry eyes and blurred vision<br>Possible hyperglycemia leading to diabetic ketoacidosis in patients with preexisting diabetes mellitus<br>Skin and soft tissue irritation due to extravasation have been observed. | Administer 1.25 mg/kg IV (maximum 125 mg) over 30 minutes on days 1, 8, and 15 of a 28-day cycle.<br>Avoid use in patients with moderate or severe hepatic impairment.<br>Do not mix or infuse with other products.<br>Do not administer as an IV push or bolus.<br>Do not shake the bag or expose to direct sunlight.<br>Monitor patients with or at risk for diabetes mellitus and withhold if blood glucose > 250 mg/dl.<br>Monitor for ocular toxicities; consider artificial tears for dry eye prevention and ophthalmologic evaluation for new or persistent eye symptoms.<br>Monitor for extravasation; symptoms may be delayed after infusion.<br>The drug is classified as an irritant (usually) or a vesicant (rarely). Apply cold for extravasation; refer to Chapter 13 for additional information.<br>(Astellas Pharma US, 2021) |
|                                             | Humanized monoclonal antibody targeting CD79b, attached to anti-microtubule agent MMAE; binds to CD79b-expressing cells, resulting in internalization and intracellular cleaving of the conjugate, releasing MMAE, which disrupts the cellular microtubule network, resulting in cell cycle arrest and apoptosis                    | Polatuzumab vedotin-piiq (Polivy®) | IV    | Relapsed or refractory DLBCL in adults, in combination with bendamustine and a rituximab product, after at least 2 prior therapies                                                                                  | Neutropenia, anemia, thrombocytopenia, peripheral neuropathy, fatigue, diarrhea, fever, anorexia, pneumonia, infusion-related reactions, opportunistic infections, progressive multifocal leukoencephalopathy, TLS, hepatotoxicity                                                                                                                         | Administer 1.8 mg/kg IV over 90 minutes every 21 days for 6 cycles in combination with bendamustine and a rituximab product. Subsequent infusions may be administered over 30 minutes if the previous infusion is tolerated.<br>Premedicate with an antihistamine and antipyretic at least 30 minutes prior to starting the infusion.<br>Administer with an 0.2- or 0.22-micron in-line filter.<br>Monitor CBC.<br>Consider prophylactic G-CSF.<br>Administer prophylaxis for <i>Pneumocystis jirovecii</i> pneumonia and herpes viruses throughout treatment.<br>Administer TLS prophylaxis for at-risk patients.                                                                                                                                                                                                                            |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                              | Mechanism of Action                                                                                                                                                                                                                                                                                                                                                           | Drug                                                   | Route | Indications                                                                                                                                                                                  | Side Effects                                                                                                                                                                                                                                                                                                                                                    | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|---------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Antibody-drug conjugate<br>( <i>Cont.</i> ) |                                                                                                                                                                                                                                                                                                                                                                               | Polatuzumab vedotin-piiq (Polivy®)<br>( <i>Cont.</i> ) |       |                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                 | Concomitant use with strong CYP3A4 inhibitors or inducers may affect dose. This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring. (Genentech, 2020c)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|                                             | Afucosylated monoclonal antibody directed against BCMA, attached to anti-microtubule agent MMAF; binds to BCMA-expressing cells, resulting in internalization and intracellular cleaving of the conjugate, releasing MMAF, which disrupts the cellular microtubule network, resulting in cell cycle arrest and apoptosis; also induces tumor cell lysis through ADCC and ADCP | Belantamab mafodotin-blmf (Blenrep™)                   | IV    | Relapsed or refractory multiple myeloma in adults who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, proteasome inhibitor, and immunomodulatory agent | Black box warning: ocular toxicity, including changes in vision, severe vision loss, and corneal ulcer<br>Ocular changes, keratopathy (corneal epithelium change on eye exam), dry eyes, blurred vision, fever, nausea, infusion-related reactions, fatigue, myelosuppression, increased creatinine, increased gamma-glutamyltransferase, embryo-fetal toxicity | Administer 2.5 mg/kg IV over 30 minutes once every 3 weeks.<br>Conduct ophthalmic exams at baseline (within 3 weeks of the first dose), prior to each dose (between 1 week after the previous dose and within 2 weeks of the next dose), and promptly for worsening symptoms.<br>Advise patients to use preservative-free lubricant eye drops at least 4 times a day, starting with the first infusion and continuing until the end of treatment.<br>Instruct patients to avoid wearing contact lenses unless directed by an ophthalmologist.<br>Vision changes may be associated with difficulty reading or driving. Advise patients to use caution when driving or operating machinery.<br>Monitor CBC at baseline and during treatment as clinically indicated.<br>Monitor patients for infusion-related reactions. Interrupt infusion and reduce the rate or permanently discontinue based on the severity of the reaction.<br>Belantamab mafodotin-blmf is available only through the Blenrep REMS program.<br>This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring. (GlaxoSmithKline, 2020) |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                              | Mechanism of Action                                                                                                                                                                                                                                                                                      | Drug                                 | Route | Indications                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Side Effects                                                                                                                                                                                                                                                                           | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|---------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|-------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Antibody-drug conjugate<br>( <i>Cont.</i> ) | Humanized monoclonal antibody targeting HER2, attached to anti-microtubule agent DM1; binds to HER2-expressing cells, resulting in internalization and intracellular cleaving of conjugate, releasing DM1, which disrupts the cellular microtubule network, resulting in cell cycle arrest and apoptosis | Ado-trastuzumab emtansine (Kadcyla®) | IV    | HER2-positive early breast cancer, as a single agent, in patients with residual invasive disease following neoadjuvant taxane and trastuzumab-based treatment<br>HER2-positive metastatic breast cancer, as a single agent, in patients who previously received trastuzumab and a taxane and have either received prior therapy for metastatic disease or experience disease recurrence during adjuvant therapy or within 6 months of completing adjuvant therapy | Fatigue, nausea, musculoskeletal pain, arthralgia, peripheral neuropathy, headache, increased transaminases, constipation, thrombocytopenia, bleeding, epistaxis, cardiotoxicity<br>Reactions such as erythema, swelling, irritation, and pain have been observed after extravasation. | Administer 3.6 mg/kg IV over 90 minutes on day 1 of a 21-day cycle.<br>If well-tolerated, subsequent infusions may be administered over 30 minutes.<br>Do not mix or infuse with other products.<br>Do not administer as an IV push or bolus.<br>Administer with an 0.2- or 0.22-micron in-line PES filter.<br>Observe patients during infusion and for at least 90 minutes following the initial dose and 30 minutes following subsequent doses for fever, chills, or other infusion-related reactions.<br>Patients may require dose modifications for increased transaminases, hyperbilirubinemia, thrombocytopenia, or cardiotoxicity (e.g., left ventricular dysfunction).<br>Monitor LVEF at baseline and at regular intervals during treatment.<br>Discontinue therapy for symptomatic congestive heart failure, ILD, pneumonitis, or nodular regenerative hyperplasia.<br>Do not substitute trastuzumab for or with ado-trastuzumab emtansine.<br>Monitor for infiltration during administration.<br>The drug is classified as an irritant (usually) or a vesicant (rarely). Apply cold for extravasation; refer to Chapter 13 for additional information.<br>This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring.<br>(Genentech, 2020a) |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                              | Mechanism of Action                                                                                                                                                                                                                                                                           | Drug                                       | Route | Indications                                                                                                                                                                                                                                                                                            | Side Effects                                                                                                                                                                                                                                                                                | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|---------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|-------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Antibody-drug conjugate<br>( <i>Cont.</i> ) | Humanized monoclonal antibody targeting HER2 attached to topoisomerase I inhibitor DXd; binds to HER2-expressing cells and is internalized with the subsequent release of DXd, which prevents religation of topoisomerase I-induced single-strand DNA breaks and damage, leading to apoptosis | Fam-trastuzumab deruxtecan-nxki (Enhertu®) | IV    | Unresectable or metastatic HER2-positive breast cancer in adults who have received 2 or more prior anti-HER2-based regimens in the metastatic setting<br>Locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma in adults who previously received a trastuzumab-containing regimen | Black box warning: ILD (pneumonitis, cough, dyspnea, fever, worsening respiratory status), embryo-fetal toxicity<br>Nausea, fatigue, vomiting, alopecia, constipation, decreased appetite, anemia, diarrhea, leukopenia, cough, thrombocytopenia, neutropenia, left ventricular dysfunction | Administer 5.4 mg/kg IV once every 3 weeks. The first dose is administered over 90 minutes; subsequent doses are administered over 30 minutes.<br>Assess for LVEF prior to initiation and at regular intervals throughout therapy. Monitor and manage signs and symptoms of LVEF. Interrupt at LVEF of 40%–45% and an absolute decrease from baseline of 10%–20%, or if LVEF < 40% with an absolute decrease > 20%, which requires permanent discontinuation if confirmed. Discontinue treatment in patients with symptomatic congestive heart failure.<br>Discontinue treatment in all patients with ≥ grade 2 ILD.<br>Monitor CBC prior to initiation and for each subsequent dose. Interrupt treatment in the presence of grade 3–4 neutropenia. Resume at ≤ grade 2 at the same dose for grade 3 and at a reduced dose for grade 4 or with the presence of febrile neutropenia.<br>Do not substitute drug for trastuzumab or ado-trastuzumab emtansine.<br>This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring.<br>(Daiichi Sankyo, 2021) |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                              | Mechanism of Action                                                                                                                                                                                                                                                                                | Drug                                                 | Route | Indications                                                                                                                                                                                   | Side Effects                                                                                                                                                                                                            | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|---------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------|-------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Antibody-drug conjugate<br>( <i>Cont.</i> ) | Human monoclonal antibody targeting CD19, attached to alkylating agent SG3199; binds to CD19-expressing cells, resulting in internalization and intracellular cleaving of the conjugate, releasing SG3199, which induces DNA inter-strand crosslinks, resulting in cell cycle arrest and apoptosis | Loncastuximab tesirine-lpyl (Zynlonta <sup>®</sup> ) | IV    | Relapsed or refractory large B-cell lymphoma (including DLBCL not otherwise specified, transformed DLBCL, and high-grade B-cell lymphoma) in adults after 2 or more lines of systemic therapy | Myelosuppression, pleural effusion, pericardial effusion, ascites, edema, infection, cutaneous reactions including rash and photosensitivity, increased GGT, hyperglycemia, elevated LFTs, nausea, musculoskeletal pain | <p>Administer at 0.15 mg/kg IV every 3 weeks for 2 cycles, then 0.075 mg/kg IV every 3 weeks for subsequent cycles.</p> <p>Administer infusion over 30 minutes on day 1 of each 3-week cycle.</p> <p>Use adjusted body weight for dosage if patients have a body mass index <math>\geq 35</math> kg/m<sup>2</sup>: adjusted body weight in kg = <math>35 \text{ kg/m}^2 \times (\text{height in meters})^2</math>.</p> <p>Premedicate with dexamethasone 4 mg twice daily for 3 days starting the day before treatment.</p> <p>Administer using 0.2- or 0.22-micron filter.</p> <p>Hold therapy for neutropenia, thrombocytopenia, edema, or effusions of grade 2 or higher.</p> <p>The drug is classified as an irritant (usually) or a vesicant (rarely). Apply cold for extravasation; refer to Chapter 13 for additional information.</p> <p>Advise pregnant women of the potential risk to a fetus.</p> <p>This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring.</p> <p>(ADC Therapeutics America, 2021)</p> |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                              | Mechanism of Action                                                                                                                                                                                                                                                                                      | Drug                                   | Route | Indications                                                                                                                                                                                         | Side Effects                                                                                                                                                                                    | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
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| Antibody-drug conjugate<br>( <i>Cont.</i> ) | Humanized monoclonal antibody targeting Trop-2, attached to topoisomerase I inhibitor SN-38; binds to Trop-2-expressing cells and is internalized with the subsequent release of SN-38, which prevents religation of topoisomerase I-induced single-strand DNA breaks and damage that leads to apoptosis | Sacituzumab govitecan-hziy (Trodelvy™) | IV    | Unresectable locally advanced or metastatic triple-negative breast cancer in adults who have received at least 2 prior therapies, at least one for metastatic disease<br>Advanced urothelial cancer | Nausea, neutropenia, diarrhea, fatigue, anemia, vomiting, alopecia, constipation, rash, decreased appetite, abdominal pain, infusion-related reactions, hypersensitivity, embryo-fetal toxicity | <p>The recommended dose is 10 mg/kg once weekly on days 1 and 8 of continuous 21-day treatment cycles until disease progression or unacceptable toxicity. The first infusion is administered over 3 hours. Subsequent infusions can be administered over 1–2 hours if prior infusions were tolerated. Observe for 30 minutes after infusions.</p> <p>Prolonged neutropenia and febrile neutropenia may require dose adjustment and G-CSF support.</p> <p>Premedicate for prevention of infusion reactions with antipyretics and H<sub>1</sub> and H<sub>2</sub> antagonists. Add corticosteroids if patients have a history of infusion-related reactions. Monitor during infusion and for at least 30 minutes after completion. Permanently discontinue if severe or life-threatening reactions occur.</p> <p>Premedicate for nausea and vomiting with a 2–3 drug combination regimen, such as dexamethasone with a 5-HT<sub>3</sub> receptor antagonist or a neurokinin-1 receptor antagonist.</p> <p>Patients who are homozygous for the UGT1A1*28 allele are at increased risk for neutropenia following initiation of sacituzumab govitecan-hziy treatment.</p> <p>This medication contains warnings for reproduction or lactation. Please refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring. (Immunomedics, 2020)</p> |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                              | Mechanism of Action                                                                                                                                                                                                                                                                                                                                       | Drug                              | Route | Indications                                                                                                                                                                            | Side Effects                                                                                                                                                                                                                                                                                   | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
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| Antibody-drug conjugate<br>( <i>Cont.</i> ) | Humanized monoclonal antibody targeting CD33, attached to calicheamicin, an agent that binds to DNA and causes direct DNA damage; binds to CD33-expressing cells, resulting in internalization and intracellular cleaving of the conjugate, releasing calicheamicin, which induces double-strand DNA breaks, resulting in cell cycle arrest and apoptosis | Gemtuzumab ozogamicin (Mylotarg™) | IV    | Newly diagnosed CD33-positive AML including pediatric patients aged $\geq 1$ month<br>Relapsed or refractory CD33-positive AML in adults and pediatric patients aged 2 years and older | Black box warning: hepatotoxicity, including sinusoidal obstruction syndrome<br>Abdominal pain, anorexia, chills, constipation, diarrhea, dyspnea, esophagitis, fever, headache, hyperbilirubinemia, hypokalemia, infection, nausea, mucositis, vomiting, weakness, infusion-related reactions | Dose is dependent on the indication, age, and regimen:<br><ul style="list-style-type: none"> <li>• Adult, newly diagnosed, induction, combination regimen, or relapsed/refractory (single agent): 3 mg/m<sup>2</sup> (maximum 4.5 mg) on days 1, 4, and 7</li> <li>• Adult, newly diagnosed, consolidation, combination regimen: 3 mg/m<sup>2</sup> (Maximum 4.5 mg) on day 1</li> <li>• Adult, newly diagnosed, induction, single agent: 6 mg/m<sup>2</sup> on day 1 and 3 mg/m<sup>2</sup> on day 8</li> <li>• Adult, newly diagnosed, continuation, single agent: 2 mg/m<sup>2</sup> on day 1 every 4 weeks for up to 8 cycles</li> </ul> For patients with leukocyte count > 30,000/mm <sup>3</sup> , cytoreduction is recommended prior to administration.<br>Premedicate with acetaminophen 650 mg PO 1 hour prior to dose, diphenhydramine 50 mg PO or IV 1 hour prior to dose, and 1 mg/kg methylprednisolone or equivalent 30 minutes prior to dose.<br>Infuse over 2 hours with an in-line 0.2-micron PES filter.<br>Protect from light; do not shake or freeze.<br>Monitor platelet counts.<br>Advise patients to report signs of infection, GI toxicities, and hypokalemia.<br>This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring.<br>(Wyeth Pharmaceuticals, 2020) |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                              | Mechanism of Action                                                                                                                                                                                                                                                                                                                                       | Drug                                            | Route | Indications                                                                                                                                                                            | Side Effects                                                                                                                                                                                                                                                                                                                      | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|---------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Antibody-drug conjugate<br>( <i>Cont.</i> ) | Humanized monoclonal antibody targeting CD22, attached to calicheamicin, an agent that binds to DNA and causes direct DNA damage; binds to CD22-expressing cells, resulting in internalization and intracellular cleaving of the conjugate, releasing calicheamicin, which induces double-strand DNA breaks, resulting in cell cycle arrest and apoptosis | Inotuzumab ozogamicin (Besponsa®)               | IV    | Relapsed or refractory B-cell precursor ALL in adults                                                                                                                                  | Black box warning: hepatotoxicity, including sinusoidal obstruction syndrome, increased risk of HSCT non-relapse mortality. Myelosuppression, infusion-related reactions, QT interval prolongation, embryo-fetal toxicity, fatigue, fever                                                                                         | Administer IV over 1 hour:<br>• Day 1: 0.8 mg/m <sup>2</sup><br>• Day 8: 0.5 mg/m <sup>2</sup><br>• Day 15: 0.5 mg/m <sup>2</sup><br>If patients achieve complete response or clinical response with incomplete count recovery, doses for subsequent cycles are adjusted to 0.5 mg/m <sup>2</sup> on days 1, 8, and 15. Dose interruptions may be necessary in subsequent cycles for neutropenia, thrombocytopenia, and elevated LFTs. Premedicate with corticosteroid, antipyretic, and antihistamine prior to administration. Monitor for at least 1 hour after infusion for infusion-related reactions. For patients with circulating lymphoblasts, administer cyto reduction to a peripheral blast count ≤ 10,000/mm <sup>3</sup> prior to infusion. Protect from light; do not freeze. This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring. (Wyeth Pharmaceuticals, 2018) |
| Radioimmunoconjugate                        | IgG1 kappa murine monoclonal antibody targeting CD20, conjugated to yttrium-90 ( <sup>90</sup> Y); beta radiation from <sup>90</sup> Y induces cellular damage by the formation of free radicals in the target and neighboring cells.                                                                                                                     | <sup>90</sup> Y-ibritumomab tiuxetan (Zevalin®) | IV    | Relapsed or refractory follicular B-cell or low-grade non-Hodgkin lymphoma<br>Follicular lymphoma in patients who achieved a complete or partial response with first-line chemotherapy | Black box warnings: serious infusion-related reactions, prolonged and severe cytopenias, cutaneous and mucocutaneous reactions, maximum radiation dosage 32 mCi (1,184 MBq)<br>Hematologic toxicity is a major side effect. Onset may be delayed and duration prolonged. Cytopenias have persisted 12 weeks after administration. | <sup>90</sup> Y-ibritumomab tiuxetan is administered on a specific regimen that includes “pre-targeting” of the tissues with rituximab first, followed by the radiolabeled isotope. Patients receive rituximab 250 mg/m <sup>2</sup> on day 1. On day 7, 8, or 9, a second dose of rituximab 250 mg/m <sup>2</sup> is administered, followed by <sup>90</sup> Y-ibritumomab tiuxetan. If platelet count ≥ 150,000/mm <sup>3</sup> , within 4 hours after rituximab infusion, administer <sup>90</sup> Y-ibritumomab tiuxetan 0.4 mCi/kg (14.8 MBq/kg) IV. If platelet count ≥ 100,000/mm <sup>3</sup> but ≤ 149,000/mm <sup>3</sup> in patients with relapsed or refractory disease, within 4 hours after rituximab infusion, administer                                                                                                                                                                                                                                                                                     |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                            | Mechanism of Action                                                                                                                                                                       | Drug                                                                   | Route | Indications                                                                                 | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|-------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|-------|---------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Radioimmuno-conjugate<br>( <i>Cont.</i> ) |                                                                                                                                                                                           | <sup>90</sup> Y-ibritumomab tiuxetan<br>(Zevalin®)<br>( <i>Cont.</i> ) |       |                                                                                             | Fatigue, nasopharyngitis, nausea, abdominal pain, asthenia, cough, diarrhea, fever, erythema multiforme, SJS, TEN, exfoliative and bullous dermatitis<br>Severe infusion-related reactions have occurred with rituximab as a component of the therapeutic regimen; premedications should be given before rituximab. See prescribing information for side effects attributable to rituximab.<br>Secondary leukemias and myelodysplastic syndrome have been reported. | <sup>90</sup> Y-ibritumomab tiuxetan 0.3 mCi/kg (11.1 MBq/kg) IV.<br>Monitor CBC weekly for up to 3 months after administration.<br>The ability to generate an immune response to vaccines after administration has not been established, nor has the safety of administration of live vaccines. It is recommended that patients not receive live vaccines.<br>This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring.<br>(Acrotech Biopharma, 2019; Casadei et al., 2016; Stefoni et al., 2016)                                                                     |
| CD123-directed cytotoxin                  | CD123-directed cytotoxin composed of recombinant human IL-3 and truncated diphtheria toxin fusion protein that inhibits protein synthesis and causes cell death in CD123-expressing cells | Tagraxofusp-erzs (Elzonris®)                                           | IV    | Blastic plasmacytoid dendritic cell neoplasm in adult and pediatric patients aged > 2 years | Black box warning: capillary leak syndrome<br>Hypersensitivity reactions, nausea, fatigue, peripheral edema, fever, weight gain<br>Laboratory abnormalities:<br><ul style="list-style-type: none"> <li>Decreases in albumin, platelets, hemoglobin, calcium, and sodium</li> <li>Increases in glucose, ALT, and AST</li> </ul>                                                                                                                                      | Administer 12 mcg/kg IV over 15 minutes once a day on days 1–5 of a 21-day cycle.<br>Premedicate with an H <sub>1</sub> antagonist, acetaminophen, a corticosteroid, and an H <sub>2</sub> antagonist prior to each infusion.<br>Prior to the first dose, serum albumin must be ≥ 3.2 g/dl.<br>Administer the first dose in the inpatient setting with patient observation. Subsequent doses can be administered in the inpatient or appropriate outpatient setting, and patients should be observed for a minimum of 4 hours after the infusion.<br>Administer via infusion syringe pump over 15 minutes.<br>Adjust dose for serum albumin, body weight changes, AST and ALT changes, and elevated creatinine. |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                               | Mechanism of Action                                                                                                                                                    | Drug                                                | Route | Indications                                                                                                                                                | Side Effects                                                                                                                                                                                                                                                                              | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|----------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|-------|------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| CD123-directed cytotoxin<br>( <i>Cont.</i> ) |                                                                                                                                                                        | Tagraxofusp-erzs<br>(Elzonris®)<br>( <i>Cont.</i> ) |       |                                                                                                                                                            |                                                                                                                                                                                                                                                                                           | See prescribing information for holding parameters for systolic blood pressure, heart rate, body temperature, and hypersensitivity reactions.<br>Preparation is a two-step process; see prescribing information. Administer medication within 4 hours of preparation.<br>Educate patients to call healthcare providers with symptoms of capillary leak syndrome.<br>This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring.<br>(Stemline Therapeutics, 2018).                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| CD22-directed cytotoxin                      | Binds to CD22 on the cell surface of B cells and is internalized, resulting in ADP-ribosylation of elongation factor 2, inhibition of protein synthesis, and apoptosis | Moxetumomab pasudotox-tdfk (Lumoxiti®)              | IV    | Relapsed or refractory hairy cell leukemia in adults who received at least 2 prior systemic therapies, including treatment with a purine nucleoside analog | Black box warning: capillary leak syndrome, hemolytic uremic syndrome<br>Infusion-related reactions, edema, nausea, fatigue, headache, fever, constipation, anemia, diarrhea, hypoalbuminemia, hypocalcemia, hypophosphatemia, elevated creatinine, ALT, AST, GGT, and alkaline phosphate | Administer 0.04 mg/kg IV over 30 minutes on days 1, 3, and 5 in a 28-day cycle for a maximum of 6 cycles, disease progression, or unacceptable toxicity.<br>Dosing is calculated based on a patient's actual body weight prior to the first dose of the first treatment cycle. A change should only be made between cycles when there is a weight change of > 10%.<br>The drug should be reconstituted with sterile water for injection. Direct the sterile water along the walls of the vial and not directly at the lyophilized cake or powder. Do not reconstitute with IV solution stabilizer. Gently swirl the vial until the solution is completely dissolved. Invert the vial to ensure all cake or powder in the vial is dissolved. Do not shake. The solution should be clear to slightly opalescent, colorless, or slightly yellow, with no visible particles. Do not use if the solution is cloudy or discolored or contains any particles. Use reconstituted solution immediately. Do not store reconstituted medication vials. |

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| Classification                              | Mechanism of Action | Drug                                                       | Route | Indications | Side Effects | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|---------------------------------------------|---------------------|------------------------------------------------------------|-------|-------------|--------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| CD22-directed cytotoxin<br>( <i>Cont.</i> ) |                     | Moxetumomab pasudotox-tdfk (Lumoxiti®)<br>( <i>Cont.</i> ) |       |             |              | <p>For drug dilution, add IV solution stabilizer to the infusion bag prior to adding the medication solution. IV solution stabilizer is packaged separately. Obtain a 50 ml 0.9% sodium chloride injection USP (normal saline) bag. Add 1 ml IV solution stabilizer to the infusion bag. Gently invert the bag to mix the solution. Do not shake. Withdraw the required volume of medication solution from the reconstituted vial(s). Inject medication into the infusion bag. Gently invert the bag to mix the solution. Do not shake. Discard partially used or empty vials of medication and IV solution stabilizer.</p> <p>After dilution, store at room temperature for up to 4 hours and refrigerated (36°F–46°F) for 24 hours. Protect from light. Do not freeze or shake. If refrigerated, allow the solution to come to room temperature for no more than 4 hours prior to administration. Administer within 24 hours of reconstitution.</p> <p>Maintain hydration during treatment. Administer 1 L of isotonic solution over 2–4 hours before and after each infusion; if patient weighs less than 50 kg, administer 500 ml.</p> <p>Monitor serum electrolytes prior to each dose and on day 8 of each cycle.</p> <p>Encourage patients to hydrate with up to 3 L of oral fluids over 24 hours on days 1–6 of every 28-day cycle. If patients weigh less than 50 kg, 2 L is recommended.</p> <p>Consider low-dose aspirin for thromboprophylaxis on days 1–8 of each 28-day cycle.</p> <p>Premedicate (30–90 minutes prior to infusion) with acetaminophen, an antihistamine (hydroxyzine or diphenhydramine), and an H<sub>2</sub> antagonist (ranitidine, famotidine, or cimetidine) prior to all infusions.</p> |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                              | Mechanism of Action | Drug                                                      | Route | Indications | Side Effects | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|---------------------------------------------|---------------------|-----------------------------------------------------------|-------|-------------|--------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| CD22-directed cytotoxin<br>( <i>Cont.</i> ) |                     | Moxetumomab pasudotox-tdfk (Lumoxiti)<br>( <i>Cont.</i> ) |       |             |              | <p>Post-infusion medication includes oral antihistamines and antipyretics for up to 24 hours following infusion. An oral corticosteroid is recommended to decrease nausea and vomiting. Patients should maintain adequate oral fluid intake.</p> <p>If patients have a <math>\geq</math> grade 2 creatinine increase (<math>&gt; 1.5 \times</math> baseline or ULN), delay administration. Resume medication when creatinine recovers to grade 1 (<math>1-1.5 \times</math> baseline or between the ULN and <math>1.5 \times</math> the ULN).</p> <p>For patients with <math>\geq</math> grade 3 creatinine increase, delay dosing and resume when recovers to baseline grade or lower.</p> <p>Not recommended in patients with severe renal impairment (creatinine clearance <math>\leq 29</math> ml/min)</p> <p>Monitor for capillary leak syndrome before each treatment; monitor weight, blood pressure, and laboratory tests, including albumin if suspected). For grade 2 capillary leak syndrome (symptomatic), treat medically and delay dosing until recovery of symptoms. For grade 3 (severe symptoms), treat medically and discontinue the medication. For grade 4 (life-threatening), provide urgent intervention and discontinue the medication. Most cases of capillary leak syndrome occur within the first 8 days of a treatment cycle but can occur throughout the cycle. The median time to resolution was 12 days.</p> <p>Monitor for hemolytic uremic syndrome before each treatment; monitor hemoglobin, platelet count, and creatinine; maintain adequate hydration. If patients develop hemolytic uremic syndrome, discontinue medication and treat with appropriate supportive measures. Most cases occur within the first 9 days of a treatment cycle but can occur throughout the cycle. The median time to resolution was 11.5 days.</p> |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                              | Mechanism of Action                                                                                                                        | Drug                                                      | Route | Indications                                                                                                                                                                                                                                                                                                                                                                                          | Side Effects                                                                                                                                                                                          | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|---------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|-------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| CD22-directed cytotoxin<br>( <i>Cont.</i> ) |                                                                                                                                            | Moxetumomab pasudotox-tdfk (Lumoxiti)<br>( <i>Cont.</i> ) |       |                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                       | There is potential for immunogenicity. Patients who tested positive for antibodies against moxetumomab pasudotox-tdfk had decreased systemic concentrations of the drug. Avoid in patients with prior history of severe thrombotic microangiopathy or hemolytic uremic syndrome. This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring. (AstraZeneca Pharmaceuticals, 2018)                                                                                                                         |
| Checkpoint inhibitors: PD-1                 | Binds to PD-1 receptor and blocks interactions with PD-L1 and PD-L2, leading to an immune response, including an antitumor immune response | Cemiplimab-rwlc (Libtayo <sup>®</sup> )                   | IV    | Metastatic or locally advanced cutaneous squamous cell carcinoma in patients who are not candidates for curative surgery or radiation<br>Metastatic NSCLC with PD-L1 expression (tumor proportion score $\geq$ 50%)<br>Locally advanced or metastatic basal cell carcinoma previously treated with a hedgehog pathway inhibitor or disease for which a hedgehog pathway inhibitor is not appropriate | Fatigue, rash, diarrhea<br>Potential for serious immune-related toxicities, including pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, dermatologic toxicities                           | Administer 350 mg IV over 30 minutes every 3 weeks for all indications. Administer as an IV infusion only. Do not administer with other medications through the same line. Administer through an IV line containing a sterile in-line or add-on 0.2 to 5-micron filter. Adjust dose for adverse effects. Treatment may be held or discontinued based on the severity of the immune-related adverse effect. This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring. (Regeneron Pharmaceuticals, 2021) |
|                                             | Binds to PD-1 receptor and blocks interactions with PD-L1 and PD-L2, leading to an immune response, including an antitumor immune response | Dostarlimab-gxly (Jemperli <sup>®</sup> )                 | IV    | dMMR recurrent or advanced endometrial cancer that has progressed on or prior to therapy with a platin-based regimen in adults<br>dMMR solid tumors that have progressed on or following prior treatment and that have no satisfactory alternative treatment options in adults                                                                                                                       | Fatigue/asthenia, anemia, diarrhea, nausea, decreased lymphocytes, decreased sodium, increased alkaline phosphatase, decreased albumin, immune-mediated adverse reactions, infusion-related reactions | For the first 4 doses, administer 500 mg IV every 3 weeks. For subsequent dosing beginning 3 weeks after the fourth dose, administer 1,000 mg IV every 6 weeks. Administer as an IV infusion over 30 minutes. Do not administer with other medications through the same line. Administer through an IV line containing a sterile in-line or add-on 0.2-micron filter.                                                                                                                                                                                                                                                                           |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                                     | Mechanism of Action                                                                                                                        | Drug                                                | Route | Indications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Side Effects                                                                                                                                                                                                                                                                 | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|----------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|-------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Checkpoint inhibitors:<br>PD-1<br>( <i>Cont.</i> ) |                                                                                                                                            | Dostarlimab-gxly<br>(Jemperli®)<br>( <i>Cont.</i> ) |       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                              | Adjust dose for adverse effects. Treatment may be held or discontinued based on the severity of the immune-related adverse effect.<br><br>This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring.<br>(GlaxoSmithKline, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                    | Binds to PD-1 receptor and blocks interactions with PD-L1 and PD-L2, leading to an immune response, including an antitumor immune response | Nivolumab<br>(Opdivo®)                              | IV    | Unresectable or metastatic melanoma<br>Metastatic NSCLC expressing PD-L1 (≥1%)<br>Unresectable malignant pleural mesothelioma<br>Intermediate- or poor-risk renal cell carcinoma<br>Relapsed or progressive cHL after autologous HSCT and brentuximab vedotin<br>Relapsed or progressive cHL after 3 or more lines of systemic therapy that included autologous HSCT<br>Relapsed or progressive cHL after 3 or more lines of systemic therapy that includes autologous HSCT<br>Squamous cell carcinoma of the head and neck after disease progression on or after platinum-based therapy<br>Locally advanced or metastatic urothelial carcinoma<br>MSI-H or dMMR metastatic colorectal cancer<br>Hepatocellular carcinoma after progression on sorafenib (monotherapy or with ipilimumab) | Fatigue, malaise, peripheral neuropathy, GI toxicities, elevated LFTs, increased creatinine, electrolyte imbalances, weakness, anemia, neutropenia, thrombocytopenia, myalgia, upper respiratory tract infection, cough, febrile reaction, immune-mediated adverse reactions | Dosing and schedule may vary based on the indication. Refer to prescribing information.<br>Administer as an IV infusion only.<br>Do not administer with other medications through the same line.<br>Administer through an IV line containing a sterile, nonpyrogenic, low-protein-binding 0.2- to 1.2-micron in-line filter.<br>When given with ipilimumab, administer nivolumab first, followed by ipilimumab on the same day.<br>Adjust dose for adverse effects. Treatment may be held or discontinued based on the severity of the immune-related adverse effect.<br><br>This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring.<br>(Bristol-Myers Squibb, 2020) |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                                     | Mechanism of Action                                                                                                                        | Drug                                       | Route | Indications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Side Effects                                                                                                                                                                                                                                                                                            | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|----------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|-------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Checkpoint inhibitors:<br>PD-1<br>( <i>Cont.</i> ) |                                                                                                                                            | Nivolumab<br>(Opdivo®)<br>( <i>Cont.</i> ) |       | Unresectable, advanced, recurrent, or metastatic esophageal cancer after prior fluoropyrimidine- and platinum-based chemotherapy<br>Advanced or metastatic gastric cancer, GEJ cancer, and esophageal adenocarcinoma, in combination with fluoropyrimidine- and platinum-containing chemotherapy<br>Resected esophageal or GEJ cancer with residual pathologic disease previously treated with neoadjuvant chemoradiation                                                                                                                                         |                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                    | Binds to PD-1 receptor and blocks interactions with PD-L1 and PD-L2, leading to an immune response, including an antitumor immune response | Pembrolizumab<br>(Keytruda®)               | IV    | Unresectable or metastatic melanoma<br>Metastatic or stage III unresectable NSCLC expressing PD-L1 (≥1%), in combination with a platinum-containing doublet<br>Head and neck squamous cell cancer<br><ul style="list-style-type: none"> <li>• Unresectable, recurrent, or metastatic disease</li> <li>• Single-agent therapy for unresectable, recurrent, or metastatic disease with PD-L1 combined positive score &gt; 1</li> <li>• Single-agent therapy after disease progression on or after platinum-containing therapy</li> </ul> Relapsed or refractory cHL | Fatigue, skin rash, hyperglycemia, metabolic imbalances (hypomagnesemia, hypocalcemia, hypophosphatemia, hypokalemia), GI toxicities, vomiting, urinary tract infection, anemia, lymphocytopenia, thrombocytopenia, elevated LFTs, increased serum creatinine, fever, immune-mediated adverse reactions | For all adult indications, administer 200 mg IV flat dose as an infusion over 30 minutes every 3 weeks or 400 mg every 6 weeks.<br>For pediatric indications, administer 2 mg/kg IV (maximum 200 mg) as an infusion over 30 minutes every 3 weeks.<br>Administer IV over 30 minutes in a line containing a sterile, nonpyrogenic, low-protein-binding 0.2- to 5-micron in-line or add-on filter.<br>Do not coadminister other medications through the same infusion line.<br>Adjust dose for adverse effects. Treatment may be held or discontinued based on the severity of the immune-related adverse effect.<br>This medication contains warnings for reproduction or lactation. Please refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring. (Merck, 2021) |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                                     | Mechanism of Action | Drug                                             | Route | Indications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Side Effects | Nursing Considerations |
|----------------------------------------------------|---------------------|--------------------------------------------------|-------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|------------------------|
| Checkpoint inhibitors:<br>PD-1<br>( <i>Cont.</i> ) |                     | Pembrolizumab<br>(Keytruda®)<br>( <i>Cont.</i> ) |       | <p>Refractory primary mediastinal large B-cell lymphoma after relapse following 2 or more lines of therapy</p> <p>Urothelial carcinoma</p> <ul style="list-style-type: none"> <li>Locally advanced or metastatic disease ineligible for cisplatin-containing therapy, with tumor combined positive score &gt; 10</li> <li>Patients ineligible for platinum-containing therapy, regardless of PD-L1 status</li> <li>Locally advanced or metastatic disease that has progressed following a platinum-containing regimen</li> <li>Locally advanced or metastatic disease that has progressed within 12 months of neoadjuvant or adjuvant platinum-containing therapy</li> <li>High-risk, nonmuscle invasive bladder cancer with carcinoma in situ unresponsive to bacillus Calmette-Guérin, with or without papillary tumors, in patients who are ineligible for or have elected not to undergo cystectomy</li> </ul> <p>Unresectable or metastatic MSI-H or dMMR solid tumors after progression and with no satisfactory alternative treatment options</p> <p>Unresectable or metastatic MSI-H or dMMR colorectal cancer, as first-line therapy</p> |              |                        |

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**TABLE 10-1.** Immunotherapy Agents *(Continued)*

| Classification                                   | Mechanism of Action | Drug                                           | Route | Indications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Side Effects | Nursing Considerations |
|--------------------------------------------------|---------------------|------------------------------------------------|-------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|------------------------|
| Checkpoint inhibitors:<br>PD-1<br><i>(Cont.)</i> |                     | Pembrolizumab<br>(Keytruda®)<br><i>(Cont.)</i> |       | <p>Gastric cancer</p> <ul style="list-style-type: none"> <li>Locally advanced or metastatic disease</li> <li>Recurrent locally advanced or metastatic gastric or GEJ adenocarcinoma with a combined positive score &gt; 1</li> <li>First-line treatment for locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma, in combination with trastuzumab, fluoropyrimidine chemotherapy, and platinum chemotherapy</li> </ul> <p>Locally advanced or metastatic esophageal or GEJ carcinoma that is unresectable or not amenable to definitive chemoradiation, either in combination with a platinum- or fluoropyrimidine-based treatment</p> <p>Recurrent and metastatic cervical cancer with a PD-L1 combined positive score &gt; 1 after progression</p> <p>Hepatocellular carcinoma previously treated with sorafenib</p> <p>Recurrent locally advanced or metastatic Merkel cell carcinoma</p> <p>Renal cell carcinoma</p> <ul style="list-style-type: none"> <li>First-line treatment in combination with axitinib</li> <li>First-line treatment in advanced disease, in combination with lenvatinib</li> </ul> |              |                        |

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**TABLE 10-1.** Immunotherapy Agents (Continued)

| Classification                            | Mechanism of Action                                                                                                                                        | Drug                                 | Route | Indications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Side Effects                                                                                                                                                                          | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                |
|-------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|-------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Checkpoint inhibitors:<br>PD-1<br>(Cont.) |                                                                                                                                                            | Pembrolizumab (Keytruda®)<br>(Cont.) |       | <p>Advanced endometrial carcinoma (not MSI-H or dMMR), in combination with lenvatinib after disease progression, in patients who are not candidates for curative surgery or radiation</p> <p>Unresectable or metastatic tumor mutational burden-high cancer after progression and with no satisfactory alternative treatment options</p> <p>Recurrent or metastatic cutaneous squamous cell carcinoma not curable by surgery or radiation</p> <p>Triple-negative breast cancer</p> <ul style="list-style-type: none"> <li>• Locally recurrent unresectable or metastatic disease, in combination with chemotherapy for tumors with a PD-L1 combined positive score &gt; 10</li> <li>• High-risk, early-stage disease, in combination with chemotherapy as neoadjuvant treatment, then continued as a single agent as adjuvant treatment after surgery</li> </ul> |                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                       |
|                                           | Inhibits PD-L1 interactions with PD-1 and B7-1 receptors, leading to an immune response, including an antitumor immune response, without inducing any ADCC | Atezolizumab (Tecentriq®)            | IV    | <p>Urothelial carcinoma</p> <ul style="list-style-type: none"> <li>• Locally advanced or metastatic disease expressing PD-L1 (≥ 5%) that is ineligible for cisplatin-containing therapy</li> <li>• Patients ineligible for platinum-containing therapy, regardless of PD-L1 status</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Fatigue, hypoalbuminemia, hyponatremia, decreased appetite, nausea, constipation, increased serum alkaline phosphatase, increased serum AST and ALT, antibody development, infection, | <p>For all indications, administer 840 mg every 2 weeks, 1,200 mg every 3 weeks, or 1,680 mg every 4 weeks.</p> <p>Administer via IV over 60 minutes. If the first infusion is tolerated, subsequent infusions may be administered over 30 minutes.</p> <p>Always administer atezolizumab prior to chemotherapy.</p> <p>Do not coadminister other drugs through the same IV line.</p> |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                                     | Mechanism of Action | Drug                                             | Route | Indications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Side Effects                                                   | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                |
|----------------------------------------------------|---------------------|--------------------------------------------------|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Checkpoint inhibitors:<br>PD-1<br>( <i>Cont.</i> ) |                     | Atezolizumab<br>(Tecentriq®)<br>( <i>Cont.</i> ) |       | <p>NSCLC</p> <ul style="list-style-type: none"> <li>First-line therapy for metastatic disease in tumors with PD-L1 expression &gt; 50% or PD-L1 stained tumor-infiltrating immune cells covering &gt; 10% of tumor area</li> <li>First-line therapy in metastatic nonsquamous disease, in combination with albumin-bound paclitaxel and carboplatin</li> <li>First-line treatment of metastatic nonsquamous disease, in combination with bevacizumab, paclitaxel, and carboplatin</li> <li>Metastatic disease that has progressed during or following platinum-containing chemotherapy</li> <li>Disease with EGFR or ALK genomic tumor aberrations that has progressed prior to receiving atezolizumab</li> </ul> <p>Unresectable or metastatic hepatocellular carcinoma, in combination with bevacizumab, in patients who have not received prior systemic therapy</p> <p>Unresectable or metastatic melanoma with BRAF V600 variation, in combination with cobimetinib and vemurafenib</p> | musculoskeletal pain, fever, immune-mediated adverse reactions | <p>Do not administer as an IV push or bolus. Adjust dose for adverse effects. Treatment may be held or discontinued based on the severity of the immune-related adverse effects.</p> <p>This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring.<br/>(Genentech, 2021g)</p> |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                                     | Mechanism of Action                                                                                                                                                          | Drug                  | Route | Indications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Side Effects                                                                                                                                                                                                                       | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|----------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|-------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Checkpoint inhibitors:<br>PD-1<br>( <i>Cont.</i> ) | Inhibits PD-L1 interactions with PD-1 and B7-1 receptors, leading to an immune response, including an antitumor immune response; also has been shown in vitro to induce ADCC | Avelumab (Bavencio®)  | IV    | Metastatic Merkel cell carcinoma<br>Urothelial carcinoma <ul style="list-style-type: none"> <li>Locally advanced or metastatic disease with progression following platinum-containing chemotherapy or disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy</li> <li>Maintenance therapy in locally advanced or metastatic disease that has not progressed with first-line platinum-containing chemotherapy</li> </ul> Advanced renal cell carcinoma, as first-line therapy in combination with axitinib | Peripheral edema, fatigue, skin rash, diarrhea, nausea, decreased appetite, lymphocytopenia, anemia, increased serum AST, increased serum ALT, musculoskeletal pain, infusion-related reactions, immune-mediated adverse reactions | For all indications, administer 800 mg every 2 weeks.<br>Administer IV over 60 minutes in a line containing a sterile, nonpyrogenic, low-protein-binding 0.2-micron in-line filter.<br>Do not coadminister other medications through the same infusion line.<br>Premedicate with an antihistamine and acetaminophen prior to each infusion.<br>Adjust dose for adverse effects. Treatment may be held or discontinued based on the severity of the immune-related adverse effects.<br>This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring.<br>(EMD Serono, 2020)                                                                                                                                |
|                                                    | Inhibits PD-L1 interactions with the PD-1 and CD80 receptors, leading to an immune response, including an antitumor immune response; also has been shown to induce ADCC      | Durvalumab (Imfinzi®) | IV    | Unresectable stage III NSCLC that has not progressed following concurrent platinum-based chemotherapy and radiation<br>Extensive-stage SCLC, as first-line therapy in combination with carboplatin and etoposide                                                                                                                                                                                                                                                                                                                                                   | Fatigue, constipation, infection, decreased appetite, nausea, peripheral edema, urinary tract infection, musculoskeletal pain, immune-mediated adverse reactions, infusion-related reactions                                       | Dosing and schedule for stage III NSCLC is as follows: <ul style="list-style-type: none"> <li>For patients weighing &gt; 30 kg, administer 10 mg/kg IV every 2 weeks or 1,500 mg every 4 weeks</li> <li>For patients weighing &lt; 30 kg, administer 10 mg/kg IV every 2 weeks.</li> </ul> Dosing and schedule for SCLC is as follows: <ul style="list-style-type: none"> <li>For patients weighing &gt; 30 kg, administer 1,500 mg IV every 3 weeks in combination with chemotherapy, then 1,500 mg IV every 4 weeks as a single agent.</li> <li>For patients weighing &lt; 30 kg, administer 20 mg/kg IV every 3 weeks in combination with chemotherapy, then 10 mg/kg IV every 2 weeks as a single agent.</li> </ul> Administer IV over 60 minutes in a line containing a sterile, low-protein-binding 0.2- or 0.22-micron in-line filter. |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                                     | Mechanism of Action                                                                                                                                                                                                                                                                                                                                                                                                                                       | Drug                                        | Route | Indications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Side Effects                                                                                                                                                                                                                                                                                                                                                                         | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
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| Checkpoint inhibitors:<br>PD-1<br>( <i>Cont.</i> ) |                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Durvalumab<br>(Imfinzi)<br>( <i>Cont.</i> ) |       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                      | Do not coadminister other medications through the same infusion line.<br>Adjust dose for adverse effects. Treatment may be held or discontinued based on the severity of the immune-related adverse effects.<br>This medication contains warnings for reproduction or lactation. Please refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring.<br>(AstraZeneca Pharmaceuticals, 2020)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| CAR T-cell immunotherapy                           | CD19-directed, genetically modified, autologous T-cell immunotherapy that binds to CD19-expressing cancer cells and healthy B cells. CD19 cellular binding results in CD28 and CD3-zeta costimulatory domains, which activate downstream signaling cascades that lead to T-cell activation, proliferation, and acquisition of effector functions and secretion of inflammatory cytokines and chemokines, leading to the killing of CD19-expressing cells. | Axicabtagene ciloleucel<br>(Yescarta®)      | IV    | <p>Relapsed or refractory large B-cell lymphoma, after 2 or more lines of systemic therapy, including:</p> <ul style="list-style-type: none"> <li>• DLBCL not otherwise specified or arising from follicular lymphoma</li> <li>• Primary mediastinal large B-cell lymphoma</li> <li>• High-grade B-cell lymphoma</li> </ul> <p>Relapsed or refractory follicular lymphoma in adults after 2 or more lines of systemic therapy</p> <p>Not indicated for the treatment of patients with primary central nervous system lymphoma</p> | Black box warning: CRS, neurotoxicity<br>Fever, hypotension, encephalopathy, tachycardia, fatigue, headache, decreased appetite, chills, diarrhea, febrile neutropenia, infections, nausea, vomiting, hypoxia, tremor, cough, dizziness, constipation, cardiac arrhythmias, hypersensitivity reactions, prolonged cytopenias, secondary malignancies, hepatitis B virus reactivation | <p>Administer after lymphodepleting regimen per package insert.</p> <p>Axicabtagene ciloleucel is for autologous use only. Confirm patient identity prior to administration.</p> <p>Premedicate with acetaminophen 650 mg PO and diphenhydramine 12.5 mg PO or IV 1 hour prior to infusion; confirm availability of tocilizumab before infusion.</p> <p>Avoid prophylactic use of systemic corticosteroids.</p> <p>Do not use a lymphodepleting filter.</p> <p>Central venous access is recommended for administration.</p> <p>Prime tubing with normal saline prior to administration.</p> <p>Infuse the entire contents of the bag within 30 minutes by gravity or peristaltic pump. The bag may be gently agitated to prevent clumping.</p> <p>Rinse tubing with normal saline and infuse at the same rate of infusion to ensure all cells are delivered.</p> <p>The bag is stable for up to 3 hours after thawing.</p> <p>Monitor patients for hypersensitivity during infusion and for signs and symptoms of CRS and neurotoxicity, which may be life threatening.</p> |

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**TABLE 10-1.** Immunotherapy Agents *(Continued)*

| Classification                      | Mechanism of Action | Drug                                           | Route | Indications | Side Effects | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|-------------------------------------|---------------------|------------------------------------------------|-------|-------------|--------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| CAR T-cell immunotherapy<br>(Cont.) |                     | Axicabtagene ciloleucel (Yescarta®)<br>(Cont.) |       |             |              | <p>CRS may occur with a median time to onset of 2 days. Provide symptomatic support, including antipyretics, oxygen, IV fluids, or vasopressors.</p> <p>Tocilizumab (an IL-6 receptor antagonist) IV over 60 minutes may be administered to manage severe or life-threatening CRS associated with CAR T-cell therapy. It may be used with corticosteroids.</p> <p>Neurotoxicity may occur with a median time to onset of 4–6 days (depending on indication) and may occur concurrent with, following the resolution of, or independent of CRS. Assess patients for headache, encephalopathy, delirium, anxiety, sleep disorders, dizziness, tremor, peripheral neuropathy, seizures, mutism, and aphasia.</p> <p>Neurotoxicity may be managed with supportive care and steroids.</p> <p>Advise patients to not drive or operate heavy machinery for up to 8 weeks following treatment.</p> <p>Axicabtagene ciloleucel can only be administered at a certified healthcare facility; patients should be monitored at least daily during the first week following infusion for signs and symptoms of CRS and neurotoxicity; patients should remain in proximity to the center for 4 weeks after infusion for follow-up and toxicity monitoring.</p> <p>Manage increased infection risk with Ig replacement therapy and antibiotic prophylaxis.</p> <p>Treatment is available only through the Yescarta and Tecartus REMS programs.</p> <p>This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring.</p> <p>(Kite Pharma, 2021b)</p> |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                               | Mechanism of Action                                                                                                                                                                                                                                                                                                                                                                                                                                       | Drug                                  | Route | Indications                                           | Side Effects                                                                                                                                                                                                                                                                                                                                                                                    | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|----------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|-------|-------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| CAR T-cell immunotherapy<br>( <i>Cont.</i> ) | CD19-directed, genetically modified, autologous T-cell immunotherapy that binds to CD19-expressing cancer cells and healthy B cells. CD19 cellular binding results in CD28 and CD3-zeta costimulatory domains, which activate downstream signaling cascades that lead to T-cell activation, proliferation, and acquisition of effector functions and secretion of inflammatory cytokines and chemokines, leading to the killing of CD19-expressing cells. | Brexucabtagene autoleucel (Tecartus®) | IV    | Relapsed or refractory mantle cell lymphoma in adults | Black box warning: CRS, neurotoxicity<br>Fever, myelosuppression, hypersensitivity reactions, hypotension, encephalopathy, fatigue, tachycardia, arrhythmia, infection, chills, hypoxia, cough, tremor, musculoskeletal pain, headache, nausea, edema, motor dysfunction, constipation, diarrhea, decreased appetite, dyspnea, rash, insomnia, pleural effusion, aphasia, hypogammaglobulinemia | Administer after lymphodepleting regimen per package insert.<br>Brexucabtagene autoleucel is for autologous use only. Confirm patient identity prior to administration.<br>Premedicate with acetaminophen and diphenhydramine 30–60 minutes prior to infusion; avoid prophylactic use of systemic corticosteroids.<br>Confirm availability of tocilizumab before infusion.<br>Do not use a lymphodepleting filter.<br>Central venous access is recommended for administration.<br>Prime tubing with normal saline prior to administration.<br>Infuse the entire contents of the bag within 30 minutes by gravity or peristaltic pump. The bag may be gently agitated to prevent clumping.<br>Rinse tubing with normal saline and infuse at the same rate of infusion to ensure all cells are delivered.<br>The bag is stable for up to 3 hours after thawing.<br>Monitor patients for hypersensitivity during infusion and for signs and symptoms of CRS and neurotoxicity, which may be life threatening.<br>CRS may occur with a median time to onset of 3 days. Provide symptomatic support, including antipyretics, oxygen, IV fluids, or vasopressors.<br>Tocilizumab (an IL-6 receptor antagonist) IV over 60 minutes may be administered to manage severe or life-threatening CRS associated with CAR T-cell therapy. It may be used with corticosteroids.<br>Neurotoxicity may occur with a median time to onset of 6 days and may occur concurrent with, following the resolution of, or independent of CRS. Assess patients for |

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**TABLE 10-1.** Immunotherapy Agents *(Continued)*

| Classification                               | Mechanism of Action | Drug                                                         | Route | Indications | Side Effects | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|----------------------------------------------|---------------------|--------------------------------------------------------------|-------|-------------|--------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| CAR T-cell immunotherapy<br>( <i>Cont.</i> ) |                     | Brexucabtagene autoleucel<br>(Tecartus®)<br>( <i>Cont.</i> ) |       |             |              | <p>headache, encephalopathy, delirium, anxiety, sleep disorders, dizziness, tremor, peripheral neuropathy, seizures, mutism, and aphasia.</p> <p>Neurotoxicity may be managed with supportive care and steroids.</p> <p>Advise patients to not drive or operate heavy machinery for up to 8 weeks following treatment.</p> <p>Brexucabtagene autoleucel may only be administered at a certified healthcare facility; patients should be monitored at least daily during the first week following infusion for signs and symptoms of CRS and neurotoxicity; patients should remain in proximity to the center for 4 weeks after infusion for follow-up and toxicity monitoring.</p> <p>Manage increased infection risk with Ig replacement therapy and antibiotic prophylaxis.</p> <p>As part of postmarketing research, if a second primary malignancy occurs after treatment, contact Kite Pharma at 844-454-5483.</p> <p>Treatment is available only through the Yescarta and Tecartus REMS programs.</p> <p>This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring.</p> <p>(Kite Pharma, 2021a)</p> |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                               | Mechanism of Action                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Drug                                 | Route | Indications                                                                                                                                                                                                                                                                                                                                                                                                                           | Side Effects                                                                                                                                                                                                                                                                                                                                                         | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
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| CAR T-cell immunotherapy<br>( <i>Cont.</i> ) | CD19-directed, genetically modified, autologous CD4 and CD8 T-cell immunotherapy that binds to CD19-expressing cancer cells and healthy B cells. CD19 cellular binding results in CD28 transmembrane, 4-1BB (CD137), and CD3-zeta costimulatory domains, which activate downstream signaling cascades that lead to T-cell activation, proliferation, and acquisition of effector functions and secretion of inflammatory cytokines and chemokines, leading to the killing of CD19-expressing cells. | Lisocabtagene maraleucel (Breyanzi®) | IV    | <p>Relapsed or refractory large B-cell lymphoma in adults after 2 or more lines of systemic therapy, including:</p> <ul style="list-style-type: none"> <li>• DLBCL not otherwise specified (including transformed DLBCL)</li> <li>• High-grade B-cell lymphoma</li> <li>• Primary mediastinal large B-cell lymphoma</li> <li>• Follicular lymphoma grade 3B</li> </ul> <p>Not indicated for the treatment of primary CNS lymphoma</p> | <p>Black box warnings: CRS, neurotoxicity</p> <p>Fevers, hypersensitivity reactions, infection, prolonged cytopenias, hypogammaglobulinemia, second primary malignancy, fatigue, musculoskeletal pain, nausea, vomiting, headache, encephalopathy, decreased appetite, diarrhea, hypotension, tachycardia, dizziness, cough, constipation, abdominal pain, edema</p> | <p>Administer after lymphodepleting regimen per package insert. Administer 2–7 days after completion of lymphodepleting therapy. Lisocabtagene maraleucel is for autologous use only. Confirm patient identity prior to administration.</p> <p>Premedicate with acetaminophen 650 mg PO and an H<sub>1</sub> antagonist 30–60 minutes prior to infusion; confirm availability of tocilizumab before infusion. Avoid the use of systemic corticosteroids.</p> <p>Keep vials of CD8 and CD4 components separate. Prepare the syringes of the CD8 component first.</p> <p>The volume to be drawn up and infused may differ for each component; do not draw up the excess volume. Gently invert vials to mix cell product until evenly resuspended. Once drawn into syringes, administer as soon as possible.</p> <p>Lisocabtagene maraleucel should be administered within 2 hours of the start of thawing.</p> <p>Do not use a lymphodepleting filter.</p> <p>Prime tubing with normal saline prior to administration and after each CD8 or CD4 component administration.</p> <p>Administer the CD8 component first. Infuse the entire contents of the syringe at 0.5 ml/min, using the closest port or Y-arm. Administer each syringe consecutively without any time between syringes.</p> <p>After CD8 component administration, flush the entire tubing with normal saline.</p> <p>Administer the CD4 component immediately after saline flush.</p> <p>Flush entire tubing with normal saline when complete.</p> <p>Monitor patients for hypersensitivity during infusion and for signs and symptoms of CRS and neurotoxicity, which may be life threatening.</p> |

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**TABLE 10-1.** Immunotherapy Agents *(Continued)*

| Classification                               | Mechanism of Action | Drug                                                    | Route | Indications | Side Effects | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
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| CAR T-cell immunotherapy<br>( <i>Cont.</i> ) |                     | Lisocabtagene maraleucel (Breyanzi)<br>( <i>Cont.</i> ) |       |             |              | <p>CRS may occur with a median time to onset of 5 days. Provide symptomatic support, including antipyretics, oxygen, IV fluids, or vasopressors.</p> <p>Tocilizumab (an IL-6 receptor antagonist) IV over 60 minutes may be administered to manage severe or life-threatening CRS associated with CAR T-cell therapy. It may be used with corticosteroids.</p> <p>Neurotoxicity may occur with a median time to onset of 8 days after infusion and may occur concurrent with, following the resolution of, or independent of CRS. Assess patients for headache, encephalopathy, delirium, anxiety, sleep disorders, dizziness, tremor, peripheral neuropathy, seizures, mutism, and aphasia.</p> <p>Neurotoxicity may be managed with supportive care and steroids.</p> <p>Advise patients to not drive or operate heavy machinery for up to 8 weeks following treatment.</p> <p>Lisocabtagene maraleucel may only be administered at a REMS-certified healthcare facility; patients should be monitored at least daily during the first week following infusion for signs and symptoms of CRS and neurotoxicity; patients should remain in proximity to the center for 4 weeks after infusion for follow-up and toxicity monitoring.</p> <p>Manage increased infection risk with Ig replacement therapy and antibiotic prophylaxis.</p> <p>If a second primary malignancy occurs after treatment, contact Bristol-Myers Squibb at 1-888-805-4555.</p> <p>Treatment is available only through a REMS program.</p> <p>This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring.</p> <p>(Bristol-Myers Squibb, 2021)</p> |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                               | Mechanism of Action                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Drug                             | Route | Indications                                                                                                                                                                                 | Side Effects                                                                                                                                                                                                                                                                                                                                          | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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| CAR T-cell immunotherapy<br>( <i>Cont.</i> ) | <p>BCMA-directed, genetically modified autologous T-cell immunotherapy.</p> <p>The CAR construct includes an anti-BCMA single-chain variable fragment-targeting domain for antigen specificity, a transmembrane domain, a CD3-zeta activation domain, and a 4-1BB (CD137) costimulatory domain. CD3-zeta signaling initiates activation and anti-tumor activity, while 4-1BB signaling enhances T-cell expansion. Antigen-specific activation of idecabtagene vicleucel results in CAR T-cell proliferation, cytokine secretion, and subsequent cytolytic killing of BCMA-expressing cells.</p> | Idecabtagene vicleucel (Abecma®) | IV    | Relapsed or refractory multiple myeloma in adults after 4 or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody | <p>Black box warnings: CRS, neurotoxicity, hemophagocytic lymphohistiocytosis/macrophage activation syndrome, prolonged cytopenia</p> <p>Fevers, infection, fatigue, musculoskeletal pain, hypogammaglobulinemia, diarrhea, nausea, encephalopathy, edema, cough, headache, decreased appetite, neutropenia, leukopenia, thrombocytopenia, anemia</p> | <p>Administer after lymphodepleting regimen per package insert. Administer 2–9 days after completion of lymphodepleting therapy. Idecabtagene vicleucel is for autologous use only. Confirm patient identity prior to administration.</p> <p>Premedicate with acetaminophen 650 mg PO and an H<sub>1</sub> antagonist 30–60 minutes prior to infusion; confirm availability of tocilizumab before idecabtagene vicleucel infusion. Avoid the use of systemic corticosteroids.</p> <p>Idecabtagene vicleucel should be administered within 1 hour of the start of thawing and is stable for 2 hours once thawed. Do not use a lymphodepleting filter. Prime tubing with normal saline prior to administration.</p> <p>Infuse entire contents of the bag within 1 hour by gravity or peristaltic pump. The bag may be gently agitated to prevent clumping.</p> <p>Rinse tubing with 30–60 ml normal saline and infuse at the same rate of infusion to ensure all cells are delivered.</p> <p>If more than one infusion bag has been received, administer all bags as directed. Do not initiate thaw of the next bag until infusion of the previous bag is complete.</p> <p>Monitor patients for hypersensitivity during infusion and for signs and symptoms of CRS and neurotoxicity, which may be life threatening.</p> <p>CRS may occur with a median time to onset of 1 day. Provide symptomatic support, including antipyretics, oxygen, IV fluids, or vasopressors.</p> <p>Tocilizumab (an IL-6 receptor antagonist) IV over 60 minutes may be administered to manage severe or life-threatening CRS associated with CAR T-cell therapy. It may be used with corticosteroids.</p> |

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**TABLE 10-1.** Immunotherapy Agents *(Continued)*

| Classification                               | Mechanism of Action | Drug                                                   | Route | Indications | Side Effects | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
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| CAR T-cell immunotherapy<br>( <i>Cont.</i> ) |                     | Idecabtagene vicleucel<br>(Abecma)<br>( <i>Cont.</i> ) |       |             |              | <p>Neurotoxicity may occur with a median time to onset of 2 days after infusion and may occur concurrent with, following the resolution of, or independent of CRS. Assess patients for headache, encephalopathy, delirium, anxiety, sleep disorders, dizziness, tremor, peripheral neuropathy, seizures, mutism, and aphasia.</p> <p>Neurotoxicity may be managed with supportive care and steroids.</p> <p>Advise patients to not drive or operate heavy machinery for up to 8 weeks following treatment.</p> <p>Idecabtagene vicleucel may only be administered at a REMS-certified healthcare facility; patients should be monitored at least daily during the first week following infusion for signs and symptoms of CRS and neurotoxicity; patients should remain in proximity to the center for 4 weeks after infusion for follow-up and toxicity monitoring.</p> <p>Manage increased infection risk with Ig replacement therapy and antibiotic prophylaxis.</p> <p>If a second primary malignancy occurs after treatment, contact Bristol-Myers Squibb at 1-888-805-4555.</p> <p>Treatment is available only through a REMS program.</p> <p>This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring.</p> <p>(Celgene, 2021a)</p> |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                               | Mechanism of Action                                                                                                                                                                                                                                                                                                                                                                                                                                                | Drug                        | Route | Indications                                                                                                                                                      | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                                           | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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| CAR T-cell immunotherapy<br>( <i>Cont.</i> ) | CD19-directed, genetically modified, autologous T-cell immunotherapy that binds to CD19-expressing cancer cells and healthy B cells. CD19 cellular binding results in 4-1BB (CD137) and CD3-zeta costimulatory domains, which activate downstream signaling cascades that lead to T-cell activation, proliferation, and acquisition of effector functions and secretion of inflammatory cytokines and chemokines, leading to the killing of CD19-expressing cells. | Tisagenlecleucel (Kymriah®) | IV    | B-cell precursor ALL in individuals aged 25 years or younger<br>Relapsed or refractory large B-cell lymphoma in adults after 2 or more lines of systemic therapy | Black box warning: CRS and neurotoxicity<br>Fever, hypotension, encephalopathy, tachycardia, fatigue, headache, decreased appetite, chills, febrile neutropenia, infections, hepatitis B virus reactivation, hypoxia, tremor, cough, nausea, vomiting, diarrhea, constipation, dizziness, cardiac arrhythmias, hypersensitivity reactions, prolonged cytopenias, hypogammaglobulinemia, second primary malignancies, bleeding episodes | Administer after lymphodepleting regimen per package insert.<br>Lymphodepleting chemotherapy may be omitted in adults with relapsed or refractory DLBCL if white blood cell count is $\leq 1,000/\text{mm}^3$ within 1 week prior to tisagenlecleucel infusion.<br>Tisagenlecleucel is for autologous use only. Confirm patient identity prior to administration.<br>Premedicate with acetaminophen and an $H_1$ antagonist 30–60 minutes prior to infusion; confirm availability of tocilizumab before infusion. Avoid prophylactic use of systemic corticosteroids.<br>Administer as an IV infusion at 10–20 ml/min (adjusted by age and volume).<br>The volume in the infusion bag ranges 10–50 ml.<br>Do not use a lymphodepleting filter.<br>Prime tubing with normal saline prior to administration.<br>Infuse the entire contents of the bag within 30 minutes by gravity or peristaltic pump.<br>The bag may be gently agitated to prevent clumping.<br>Rinse tubing with 10–30 ml of normal saline and infuse at the same infusion rate to ensure all cells are delivered.<br>Monitor patients for hypersensitivity during infusion and for signs and symptoms of CRS and neurotoxicity, which may be life threatening.<br>CRS may occur with a median time to onset of 3 days. Provide symptomatic support, including antipyretics, oxygen, IV fluids, or vasopressors.<br>Tocilizumab (an IL-6 receptor antagonist) IV over 60 minutes may be administered to manage severe or life-threatening CRS associated with CAR T-cell therapy. It may be used with corticosteroids. |

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**TABLE 10-1.** Immunotherapy Agents *(Continued)*

| Classification                      | Mechanism of Action | Drug                                     | Route | Indications | Side Effects | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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| CAR T-cell immunotherapy<br>(Cont.) |                     | Tisagenlecleucel<br>(Kymriah)<br>(Cont.) |       |             |              | <p>Neurotoxicity may occur with a median time to onset of 6 days after infusion (range 1–359 days) and may occur concurrent with, following the resolution of, or independent of CRS. Assess patients for headache, encephalopathy, delirium, anxiety, sleep disorders, dizziness, tremor, peripheral neuropathy, seizures, mutism, and aphasia.</p> <p>Neurotoxicity may be managed with supportive care and steroids.</p> <p>Advise patients to not drive or operate heavy machinery for up to 8 weeks following treatment.</p> <p>Tisagenlecleucel may only be administered at a certified healthcare facility. Patients should be monitored 2–3 times during the first week following infusion for signs and symptoms of CRS and neurotoxicity. Patients should remain in proximity to the center for 4 weeks after infusion for follow-up and toxicity monitoring.</p> <p>Manage increased infection risk with Ig replacement therapy and antibiotic prophylaxis.</p> <p>Treatment is available only through a REMS program.</p> <p>This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring.</p> <p>(Novartis Pharmaceuticals, 2021)</p> |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification     | Mechanism of Action                                                                                                                                                                                                                                                                                               | Drug                       | Route                                   | Indications                                                                                                                                                                                                                                                  | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
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| Cytokines:<br>IFNs | Stimulates secretion of proteins in response to foreign invasion in the body, which activates a cascade, suppressing cell proliferation, enhancing phagocytic activity of macrophages, augmenting specific cytotoxicity of lymphocytes for target cells, and inhibiting viral replication in virus-infected cells | IFN alfa-2b<br>(Intron® A) | IM, IV,<br>SC, or<br>intrale-<br>sional | AIDS-related Kaposi sarcoma<br>Chronic myeloid leukemia<br>Hairy cell leukemia<br>Follicular lymphoma<br>Cutaneous T-cell lymphoma<br>Melanoma, surgically treated<br>with a high risk of systemic<br>recurrence<br>Renal cell carcinoma<br>Carcinoid tumors | Common: alopecia,<br>decreased weight,<br>abdominal pain, diar-<br>rhea, decreased appe-<br>tite, anorexia, nausea,<br>vomiting, neutrope-<br>nia, increased liver<br>enzymes, arthral-<br>gia, myalgia, asthenia,<br>headache, depression,<br>fatigue, fever, flu-like<br>symptoms, chills<br>Serious: cardiac dys-<br>rhythmia, cardiomy-<br>opathy, hypotension,<br>myocardial infarction,<br>supraventricular<br>arrhythmia, tachycar-<br>dia, Raynaud disease,<br>vasculitis, GI hemor-<br>rhage, pancreatitis,<br>anemia, aplastic ane-<br>mia, thrombocytope-<br>nia, hepatic enceph-<br>alopathy, liver failure,<br>functional vision loss,<br>optic disc edema,<br>optic neuritis, retinal<br>hemorrhage, retinopa-<br>thy, thrombosis of ret-<br>inal vein or artery, sui-<br>cidal thoughts, sui-<br>cide, obliterative bron-<br>chiolitis, pneumonia,<br>pneumonitis, pneu-<br>mothorax, pulmonary<br>embolism, pulmonary<br>hypertension, pulmo-<br>nary infiltrate, sarcoid-<br>osis | The induction dosage is 20 million IU/m <sup>2</sup> IV<br>for 5 consecutive days/week for 4 weeks.<br>The maintenance dosage is 10 million IU/m <sup>2</sup><br>SC 3 times/week for 48 weeks.<br>Route of administration depends on indica-<br>tion.<br>Monitor CBC, liver panel, thyroid function<br>studies (thyroid-stimulating hormone, thy-<br>roxine), and for side effects listed.<br>Discuss depression with patients; always<br>ask patients if they have suicidal or homi-<br>cidal thoughts.<br>(Merck, 2019) |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                      | Mechanism of Action                                                                                                                                                                                                       | Drug                     | Route | Indications                                                                                                                                                                                         | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                                                         | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
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| Cytokines: IFNs<br>( <i>Cont.</i> ) | Binds to cell surface receptors and is classified as a type 2 IFN; enhances oxidative metabolism of macrophages, ADCC, activation of NK cells, and expression of Fc receptors and major histocompatibility antigens       | IFN gamma (Actimmune®)   | SC    | To reduce the frequency and severity of serious infections associated with chronic granulomatous disease<br><br>To delay time to disease progression in patients with severe malignant osteoporosis | Common: flu-like symptoms, fever, chills, myalgia, fatigue, neutropenia, thrombocytopenia, liver enzyme elevation, rash, diarrhea, vomiting, nausea, arthralgia<br><br>Serious: exacerbations of underlying cardiac disease, hepatic insufficiency, pancreatitis with death, asthenia, chest pain, upper respiratory tract infection, muscle spasm, pain, confusion, depression, hallucination, mental status decrease, atopic dermatitis, urticaria | Administer 50 mcg/m <sup>2</sup> SC in patients with body surface area > 0.5 m <sup>2</sup> and 1.5 mcg/kg SC in patients with body surface area ≤ 0.5 m <sup>2</sup> three times weekly.<br>Monitor CBC, chemistries, LFTs, and urinalysis prior to treatment and every 3 months following treatment.<br>Assess for signs and symptoms of infection. Report new symptoms immediately. Symptoms will be most intense at the beginning of treatment and can wane in intensity as treatment continues.<br>(Horizon Therapeutics, 2021)                                                                             |
| Cytokines: ILs                      | Human recombinant IL-2; exact mechanism unknown, but causes induction of lymphokine-activated killer cells, NK cells, and IFN gamma production; inhibits tumor growth by stimulating growth and activity of T and B cells | Aldesleukin (Proleukin®) | IV    | Metastatic melanoma<br>Metastatic renal cell carcinoma                                                                                                                                              | Black box warnings: cardiopulmonary disease, CNS toxicity, capillary leak syndrome, infections<br><br>Common: hypotension, peripheral edema, tachycardia, vasodilation, pruritus, rash, diarrhea, loss of appetite, nausea, vomiting, anemia, thrombocytopenia, hyperbilirubinemia, asthenia, confusion, somnolence, oliguria, elevated serum creatinine, dyspnea, fever, infections, malaise, shivering                                             | Dosing is based on patient weight. Administer 600,000 IU/kg (0.037 mg/kg) IV every 8 hours for 14 doses.<br>Repeat administration after a rest period of 9 days.<br>The drug must be administered in a center with cardiac monitoring capability and intensive care if needed.<br>Administer under the supervision of a qualified physician.<br>Monitor for acute signs of infection and side effects.<br>Monitor weight, urine output, bowel movements, blood pressure, heart rate, temperature, respiratory rate, and oxygen saturation during therapy.<br>Administer supportive medications for side effects. |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                                      | Mechanism of Action                                                                                                                                 | Drug                                            | Route | Indications                                                                         | Side Effects                                                                                                                                                                                                          | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
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| Cytokines: ILs<br>( <i>Cont.</i> )                  |                                                                                                                                                     | Aldesleukin<br>(Proleukin®)<br>( <i>Cont.</i> ) |       |                                                                                     | Serious: capillary leak syndrome, hypotension, myocardial infarction, supraventricular tachycardia, ventricular tachycardia, acute renal failure, anuria, ARDS, apnea, intubation, respiratory failure, fever, sepsis | Patients need central line access while on high-dose therapy because they need IV medications to support blood pressure. These pressor support medications have vesicant properties.<br>(Clinigen, 2019)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Miscellaneous:<br>Autologous cellular immunotherapy | The precise mechanism of action unknown; induction of immune response targeted against an antigen, PAP, which is expressed on prostate cancer cells | Sipuleucel-T<br>(Provenge®)                     | IV    | Asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer | Common adverse effects: chills, fatigue, fever, back pain, nausea, joint aches, headache<br>Serious: hemorrhagic and ischemic stroke, deep vein thrombosis, pulmonary embolism                                        | The minimum dose is 50 million autologous CD54+ cells activated with PAP-GM-CSF. Three total doses are given in approximately two-week intervals.<br>Premedicate with PO acetaminophen and an antihistamine 30 minutes prior to infusion to reduce or mitigate infusion-related reactions.<br>Administer over 60 minutes.<br>Treatment must be administered within 3 hours once at room temperature.<br>Do not use a cell filter.<br>Observe patients for at least 30 minutes following each infusion.<br>Monitor for signs and symptoms of thrombosis and cerebrovascular events.<br>Use universal precautions when handling to reduce the potential risk of transmitting infectious diseases.<br>(Dendreon, 2017) |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                  | Mechanism of Action                                                                                                                                                                          | Drug                     | Route | Indications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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| Miscellaneous: Immunomodulators | Analog of thalidomide that inhibits proliferation and induces apoptosis of malignant hematopoietic cells; causes immunomodulatory effects, such as activation and increase in T and NK cells | Lenalidomide (Revlimid®) | PO    | <p>Multiple myeloma, in combination with dexamethasone</p> <p>Multiple myeloma, as maintenance following autologous HSCT</p> <p>Transfusion-dependent anemia due to myelodysplastic syndromes associated with a 5q deletion abnormality, with or without additional cytogenetic abnormalities</p> <p>Relapsed or progressed mantle cell lymphoma after 2 prior therapies, 1 of which included bortezomib</p> <p>Previously treated marginal zone lymphoma in adults, in combination with a rituximab product</p> <p>Previously treated follicular lymphoma in adults, in combination with a rituximab product</p> | <p>Black box warning: teratogenicity, hematologic toxicity, thromboembolic events</p> <p>Common: diarrhea, anemia, constipation, peripheral edema, neutropenia, fatigue, back pain, nausea, asthenia, insomnia, hypokalemia, rash, cataracts, lymphopenia, dyspnea, deep vein thrombosis, hyperglycemia, leukopenia</p> <p>Serious: embryo-fetal toxicity, hematologic toxicity, venous and arterial thromboembolism, increased mortality in patients with CLL, second primary malignancies, hepatotoxicity, severe cutaneous reactions (e.g., SJS), TLS, tumor flare reactions, impaired stem cell mobilization, thyroid disorders, early mortality in patients with mantle cell lymphoma</p> | <p>Multiple myeloma:</p> <ul style="list-style-type: none"> <li>For combination therapy with dexamethasone, the dosage is 25 mg once daily on days 1–21 of repeated 28-day cycles.</li> <li>For maintenance therapy following autologous HSCT, the dosage is 10 mg once daily continuously on days 1–28 of repeated 28-day cycles.</li> </ul> <p>For myelodysplastic syndrome, the dosage is 10 mg once daily.</p> <p>For mantle cell lymphoma, the dosage is 25 mg once daily on days 1–21 of repeated 28-day cycles.</p> <p>For marginal zone lymphoma, the dosage is 20 mg once daily for days 1–21 of a 28-day treatment cycle, in combination with rituximab, for up to 12 cycles.</p> <p>For follicular lymphoma, the dosage is 20 mg once daily for 21 days of a 28-day treatment cycle, in combination with rituximab, for up to 12 cycles.</p> <p>The drug is available in 2.5, 5, 10, 15, 20, and 25 mg capsules.</p> <p>Adjust dose for renal dysfunction.</p> <p>The drug should be taken orally at the same time each day with or without food; advise patients that capsules should be swallowed whole with water and should not be opened, broken, or chewed.</p> <p>Lenalidomide is only available through a REMS program.</p> <p>Patients taking concomitant therapies, such as erythropoietin-stimulating agents or estrogen-containing therapies, may have an increased risk of thrombosis.</p> <p>Patients must not donate blood during treatment and for 1 month following treatment.</p> <p>The drug is teratogenic and should not be used in women who are or may become pregnant.</p> |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                                         | Mechanism of Action                                                                                      | Drug                                            | Route | Indications                                                                                                                                                                                                                                                                                                                                                            | Side Effects                                                                                                                                                                                                                                                                                                                                                                                  | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|--------------------------------------------------------|----------------------------------------------------------------------------------------------------------|-------------------------------------------------|-------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Miscellaneous:<br>Immunomodulators<br>( <i>Cont.</i> ) |                                                                                                          | Lenalidomide<br>(Revlimid®)<br>( <i>Cont.</i> ) |       |                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                               | This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring.<br>(Celgene, 2019b)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|                                                        | Analog of thalidomide that inhibits proliferation and induces apoptosis of malignant hematopoietic cells | Pomalidomide<br>(Pomalyst®)                     | PO    | Multiple myeloma in patients who have received at least 2 prior therapies, including lenalidomide and bortezomib, and have demonstrated disease progression on or within 60 days of completion of the previous therapy<br>AIDS-related Kaposi sarcoma in adults after failure of highly active antiretroviral therapy<br>Kaposi sarcoma in adults who are HIV-negative | Black box warning: teratogenicity, thromboembolic events<br>Common: fatigue, asthenia, neutropenia, anemia, constipation, nausea, diarrhea, dyspnea, upper respiratory tract infection, back pain, fever<br>Serious: embryo-fetal toxicities, venous thromboembolism, hematologic toxicity, hypersensitivity reactions, dizziness, confusion, neuropathy, risk of second primary malignancies | Dosage is 4 mg/day on days 1–21 of repeated 28-day cycles in combination with dexamethasone until disease progression.<br>The drug is available in 1, 2, 3, and 4 mg capsules.<br>Advise patients that capsules should be swallowed whole with water, with or without food, and should not be opened, broken, or chewed.<br>Avoid use in patients with serum creatinine > 3 mg/dl.<br>The drug is only available through a REMS program.<br>Patients must not donate blood during treatment and for 1 month following treatment.<br>This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring.<br>(Celgene, 2020) |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                                         | Mechanism of Action                                                                                | Drug                    | Route | Indications                                                         | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
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| Miscellaneous:<br>Immunomodulators<br>( <i>Cont.</i> ) | Not fully understood; possesses immunomodulatory, anti-inflammatory, and antiangiogenic properties | Thalidomide (Thalomid®) | PO    | Newly diagnosed multiple myeloma, in combination with dexamethasone | <p>Black box warning: teratogenicity, thromboembolic events</p> <p>Common: fatigue, hypocalcemia, edema, constipation, peripheral neuropathy, dyspnea, muscle weakness, leukopenia, neutropenia, rash/desquamation, confusion, anorexia, nausea, anxiety/agitation, asthenia, tremor, fever, weight loss, thrombosis/embolism, motor neuropathy, weight gain, dizziness, dry skin</p> <p>Serious: ischemic heart disease in patients treated in combination with dexamethasone, dizziness and orthostatic hypotension, neutropenia, thrombocytopenia, bradycardia, SJS, TEN, seizures, TLS, hypersensitivity reaction, increased HIV viral load</p> | <p>Dosage is 200 mg once daily in combination with dexamethasone 40 mg/day on days 1–4, 9–12, and 17–20 of a 28-day cycle. Doses should be taken once daily with water, preferably at bedtime and at least 1 hour after a meal.</p> <p>The drug is available in 50, 100, 150, and 200 mg capsules.</p> <p>Examine patients every 3 months for signs of peripheral neuropathy.</p> <p>The drug is only available through a REMS program.</p> <p>Patients must not donate blood during treatment and for 1 month following treatment.</p> <p>The drug is teratogenic; avoid use in pregnant women and women of childbearing potential.</p> <p>This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring. (Celgene, 2021b)</p> |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                   | Mechanism of Action                                                                                                                                                | Drug                            | Route | Indications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Side Effects                                                                                                                                                                                                                                                                                                                                         | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
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| Monoclonal antibody:<br>Chimeric | Blocks the binding of ligands to EGFR, resulting in the inhibition of cell growth and induction of apoptosis; also mediates ADCC against certain human tumor types | Cetuximab (Erbix <sup>®</sup> ) | IV    | <p><i>KRAS</i> wild-type EGFR-expressing metastatic colorectal cancer in combination with chemotherapy; not indicated when results of the <i>RAS</i> variation tests are unknown</p> <p>Recurrent or metastatic squamous head and neck cancer after platinum-based chemotherapy failure</p> <p>Locally or regionally advanced squamous head and neck cancer in combination with radiation therapy</p> <p>Locoregional or metastatic squamous head and neck cancer in combination chemotherapy</p> | <p>Black box warning: cardiopulmonary arrest, infusion-related reactions</p> <p>Fatigue, pain, peripheral neuropathy, headache, insomnia, weight loss, skin toxicities (e.g., acneiform rash, nail changes), hypomagnesemia, dehydration, GI toxicities, elevated LFTs, weakness, dyspnea, cough, fever, pharyngitis, infusion-related reactions</p> | <p>Administer 400 mg/m<sup>2</sup> initial dose as a 120-minute IV infusion.</p> <p>The maintenance dosage is 250 mg/m<sup>2</sup> weekly over 60 minutes. The maximum infusion rate is 10 mg/min.</p> <p>Initiate cetuximab 1 week prior to the start of radiation therapy.</p> <p>Complete cetuximab 1 hour prior to platinum-based therapy with a 5-fluorouracil and FOLFIRI regimen.</p> <p>Administer with a 0.22-micron in-line filter.</p> <p>Premedicate with antihistamine.</p> <p>Treatment for anaphylactic reactions should be available as needed during and for 1 hour after infusion.</p> <p>Monitor serum electrolytes (e.g., magnesium, potassium, calcium) during and up to 8 weeks after treatment.</p> <p>Monitor for dermatologic toxicities and advise patients to wear sunscreen. Monitor for preexisting cardiac disease or worsening or new cardiac symptoms.</p> <p>Do not administer as an IV push or bolus.</p> <p>This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring.</p> <p>(Eli Lilly and Company, 2021)</p> |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                                       | Mechanism of Action                                                                                                                                                                                                                        | Drug                        | Route | Indications                                                                                                                                                                                                                                                                                                                           | Side Effects                                                                                                                                                          | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
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| Monoclonal antibody:<br>Chimeric<br>( <i>Cont.</i> ) | Chimeric monoclonal antibody directed against CD38 expressed on multiple myeloma cells; exerts antitumor activity via ADCC, CDC, and ADCP; activates NK cells in the absence of CD38+ target cells and suppresses CD38+ regulatory T cells | Isatuximab-irfc (Sarclisa®) | IV    | Multiple myeloma, in combination with pomalidomide and dexamethasone, in adults who have received at least 2 prior therapies, including lenalidomide and a proteasome inhibitor<br>Relapsed or refractory multiple myeloma, in combination with carfilzomib and dexamethasone, in adults who have received 1–3 prior lines of therapy | Neutropenia, myelosuppression, infusion-related reactions, pneumonia, upper respiratory tract infection, diarrhea, second primary malignancies, embryo-fetal toxicity | Administer 10 mg/kg IV every week for 4 weeks followed by every 2 weeks, in combination with pomalidomide and dexamethasone or in combination with carfilzomib and dexamethasone.<br>Premedicate with dexamethasone, acetaminophen, H <sub>2</sub> antagonists, and diphenhydramine.<br>If a reaction occurs, treat patients as indicated. Discontinue treatment permanently for grade 3–4 reactions.<br>Monitor patients with neutropenia for signs of infection. Colony-stimulating factors may be needed for the improvement of neutrophil count.<br>Monitor patients for the development of second primary malignancies.<br>The drug can interfere with serologic testing (indirect antiglobulin test). Type and screen patients prior to starting treatment and inform the blood bank that patients have received isatuximab-irfc.<br>The drug may interfere with the assays used to monitor myeloma protein, affecting the determination of complete response.<br>This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring.<br>(Sanofi-Aventis U.S., 2021) |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                                       | Mechanism of Action                                                                                                                               | Drug                                                                                                  | Route | Indications                                                                                  | Side Effects                                                                                                                                                                                                                                                                                           | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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| Monoclonal antibody:<br>Chimeric<br>( <i>Cont.</i> ) | Binds to the anti-gen CD20 on B cells, leading to B-cell lysis                                                                                    | Rituximab (Rituxan®), Rituximab-abbs (Truxima®), Rituximab-arrx (Riabni™), Rituximab-pvvr (Ruxience®) | IV    | CD20-positive CLL<br>CD20-positive non-Hodgkin lymphoma                                      | Black box warnings: infusion-related reactions within 24 hours of infusion, TLS<br>Severe mucocutaneous reactions, progressive multifocal leukoencephalopathy<br>Adverse reactions: fatigue, chills, neuropathy, nausea, lymphocytopenia, anemia, infection, weakness, infusion-related reactions, TLS | For non-Hodgkin lymphoma, administer 375 mg/m <sup>2</sup> IV according to schedule for specific diagnosis (see prescribing information).<br>For CLL, administer 375 mg/m <sup>2</sup> in cycle 1 and 500 mg/m <sup>2</sup> in cycles 2–6.<br>With first administration in patients with high disease burden, consider stepped-up dosing: 50 mg on day 1, 150 mg on day 2, and the remainder of the 375 mg/m <sup>2</sup> on day 3.<br>Do not administer as an IV push or bolus.<br>Premedicate with acetaminophen and an antihistamine prior to each infusion.<br>Adjust dose for adverse effects. Treatment may be held or discontinued based on the severity of the adverse effects.<br>Monitor hepatitis B serologies. If patients have a history of hepatitis B, advise them to report any signs or symptoms of an active infection.<br>Advise patients to avoid vaccines. Administration of non-live vaccines should take place at least 4 weeks prior to 2-week treatment.<br>Instruct patients to report any skin toxicities.<br>This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring.<br>(Amgen, 2020a; Genentech, 2020d, 2021f; Pfizer; 2020; Teva Pharmaceuticals, 2019b; Winkler et al., 1999) |
|                                                      | Binds to the antigen CD20 and is combined with hyaluronidase. Hyaluronidase increases permeability of the SC tissue by depolymerizing hyaluronan. | Rituximab and hyaluronidase (Rituxan Hycela®)                                                         | SC    | CD20-positive CLL<br>CD20-positive non-Hodgkin lymphoma<br>CD20-positive follicular lymphoma | Black box warnings: hepatitis B virus reactivation, severe mucocutaneous reactions, progressive multifocal leukoencephalopathy<br>Adverse effects: neutropenia, anemia,                                                                                                                                | All patients receive at least one full dose of rituximab IV before receiving the SC dose of rituximab and hyaluronidase.<br>For CLL, administer 1,600 mg rituximab and 26,800 units hyaluronidase SC over 7 minutes.<br>For non-Hodgkin lymphoma and follicular lymphoma, administer 1,400 mg rituximab and 23,400 units hyaluronidase SC over 5 minutes.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                                       | Mechanism of Action                                                                                                                                                                                           | Drug                                                                 | Route | Indications                                                                                                                                                                                | Side Effects                                                                                                                                                                                                                                                                             | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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| Monoclonal antibody:<br>Chimeric<br>( <i>Cont.</i> ) |                                                                                                                                                                                                               | Rituximab and hyaluronidase<br>(Rituxan Hycela®)<br>( <i>Cont.</i> ) |       |                                                                                                                                                                                            | hypersensitivity reaction, nausea, constipation, diarrhea, fatigue, TLS, bowel obstruction or perforation, embryo-fetal toxicities                                                                                                                                                       | Rituximab and hyaluronidase is for SC administration only.<br>Premedicate with acetaminophen and antihistamine before each dose. Consider premedication with corticosteroid.<br>Adjust dose for adverse effects. Treatment may be held or discontinued based on the severity of the adverse effects.<br>Monitor hepatitis B serologies. If patients have a history of hepatitis B, advise them to report any signs or symptoms of an active infection.<br>Advise patients to avoid vaccines. Administration of non-live vaccines should take place at least 4 weeks prior to 2-week treatment.<br>Instruct patients to report any skin toxicities.<br>This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring.<br>(Genentech, 2017b, 2021) |
|                                                      | Binds to HER2 leading to ADCC; also found in vitro increased binding to activating Fc receptor FCGR3A and decreases binding to inhibitory Fc receptor FCGR2B, leading to enhanced ADCC and NK cell activation | Margetuximab-cmkb<br>(Margenza®)                                     | IV    | Metastatic HER2-positive breast cancer, in combination with chemotherapy, in adults who have received 2 or more prior anti-HER2 regimens, at least one of which was for metastatic disease | Black box warning: left ventricular dysfunction, embryo-fetal toxicity<br>Infusion-related reactions, fatigue, nausea, vomiting, diarrhea, constipation, headache, fever, alopecia, abdominal pain, peripheral neuropathy, arthralgia, myalgia, cough, palmar-plantar erythrodysesthesia | After chemotherapy is complete, administer as an IV infusion at 15 mg/kg over 120 minutes for the initial dose, then over at least 30 minutes, every 3 weeks.<br>Decrease rate for mild or moderate infusion-related reactions. Interrupt for dyspnea or significant hypotension. Discontinue if infusion reactions are severe or life-threatening.<br>Assess LVEF at baseline and regularly during treatment. Hold therapy if LVEF is below institutional limits of normal or $\geq 16\%$ absolute decrease.<br>This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring.<br>(MacroGenics, 2020)                                                                                                                                           |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                  | Mechanism of Action                                                                                                                                                                                                  | Drug                                                  | Route | Indications                                                                                                                                                                                                                                                                                                                                                                  | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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| Monoclonal antibodies:<br>Human | Binds to CD38, resulting in apoptosis via Fc-mediated cross-linking and immune-mediated tumor cell death by CDC, ADCC, and ADCP                                                                                      | Daratumumab (anti-CD38 antibody; Darzalex®)           | IV    | Newly diagnosed, relapsed, or refractory multiple myeloma in adults<br>Newly diagnosed multiple myeloma, in combination with other therapy<br>Relapsed or refractory multiple myeloma, as monotherapy or in combination with other therapy<br>Newly diagnosed light-chain amyloidosis, in combination with bortezomib, cyclophosphamide, and dexamethasone                   | Fatigue, nausea, lymphocytopenia, neutropenia, anemia, back pain, cough, fever, infusion-related reactions, asthenia, diarrhea, constipation, decreased appetite, vomiting, muscle spasms, arthralgia, fever, chills, dizziness, insomnia, cough, dyspnea, peripheral edema, peripheral sensory neuropathy, bronchitis, pneumonia, upper respiratory tract infection<br>Potential treatment-related toxicities, including anaphylactic infusion-related reactions, interference with crossmatching and blood cell antibody screening, thrombocytopenia | The drug interferes with serologic testing. Obtain a type and screen prior to treatment. Daratumumab binds to CD38 on RBCs and results in a positive indirect Coombs test. Positive Coombs test may occur up to 6 months after final administration. Notify the transfusion center that patients have received daratumumab. Administer 16 mg/kg based on actual body weight. Titrate per package insert based on volume and dose. Use a 0.22- or 0.2-micron in-line, nonpyrogenic, low-protein-binding PES filter. Do not administer as an IV push or bolus. Administer weekly for 8 doses (weeks 1–8), then every 2 weeks (weeks 9–24), and then every 4 weeks (starting week 25) until disease progression. Premedicate with PO or IV dexamethasone 20 mg, PO antipyretic, and PO or IV antihistamine. Educate patients to report symptoms of infection and easy bruising or bleeding. (Janssen Biotech, 2020a) |
|                                 | Binds to CD38, resulting in apoptosis via Fc-mediated cross-linking and immune-mediated tumor cell death by CDC, ADCC, and ADCP. Hyaluronidase increases permeability of the SC tissue by depolymerizing hyaluronan. | Daratumumab and hyaluronidase-fihj (Darzalex Faspro®) | SC    | Newly diagnosed multiple myeloma, in combination with bortezomib, melphalan, and prednisone, in patients who are ineligible for autologous HSCT<br>Newly diagnosed multiple myeloma, in combination with lenalidomide and dexamethasone, in patients who are ineligible for autologous HSCT<br>Relapsed or refractory multiple myeloma, in combination with lenalidomide and | Fatigue, nausea, lymphocytopenia, neutropenia, anemia, back pain, cough, hypersensitivity and other administration reactions (skin reactions at or near the injection site), asthenia, diarrhea, constipation, decreased appetite, vomiting, muscle spasms, arthralgia, fever, chills, dizziness, insomnia, cough,                                                                                                                                                                                                                                     | The drug interferes with serologic testing. Daratumumab binds to CD38 on RBCs and results in a positive indirect Coombs test. Obtain a type and screen prior to the start of treatment. Positive Coombs test may occur up to 6 months after the final dose. Notify the transfusion center that patients have received daratumumab. Drug combination allows for SC dosing of daratumumab. Premedicate with a corticosteroid, acetaminophen, and an H <sub>1</sub> antagonist. Premedication may be discontinued after the first three doses if no major systemic administration-related reactions occur.                                                                                                                                                                                                                                                                                                           |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                                      | Mechanism of Action                                 | Drug                                                                   | Route | Indications                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Side Effects                                                                                                                                                                                                                                                                           | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
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| Monoclonal antibodies:<br>Human<br>( <i>Cont.</i> ) |                                                     | Daratumumab and hyaluronidase-fihj (Darzalex Faspro® ( <i>Cont.</i> )) |       | dexamethasone, in patients who have received at least 1 prior therapy<br>Multiple myeloma, in combination with bortezomib and dexamethasone, in patients who have received at least one prior therapy<br>Multiple myeloma, as monotherapy, in patients who have received at least 3 prior lines of therapy, including a proteasome inhibitor and an immunomodulatory agent, or in patients who are double refractory to a proteasome inhibitor and an immunomodulatory agent | dyspnea, peripheral edema, peripheral sensory neuropathy, bronchitis, pneumonia, upper respiratory tract infection<br>Potential treatment-related toxicities, including anaphylactic reaction, interference with crossmatching and blood cell antibody screening, and thrombocytopenia | The dosage is 1,800 mg daratumumab and 30,000 units hyaluronidase SC, according to the recommended schedule. The schedule is dependent on whether treatment is a combination or monotherapy.<br>Inject 15 ml of the drug into the SC tissue of the abdomen, approximately 3 in. (7.5 cm) to the right or left of the navel, over approximately 3–5 minutes. No data are available on injecting other sites of the body.<br>Rotate injection sites for successive injections.<br>Never inject into areas where the skin is red, bruised, tender, or hard or areas with scars. Pause or slow delivery rate if patients experience pain. In the event pain is not alleviated by pausing or slowing down the delivery rate, a second injection site may be used on the opposite side of the abdomen to deliver the remainder of the dose.<br>Skin reactions at or near the injection site can occur. Symptoms may include itching, swelling, bruising, or redness. These reactions can occur more than 24 hours after an injection.<br>Patients should be monitored after the first and second SC dose if they have never received IV daratumumab. The median time to onset of a systemic administration-related reaction is 3.7 hours.<br>Educate patients to report symptoms of infection and easy bruising or bleeding. (Janssen Biotech, 2020b) |
|                                                     | Binds to RANKL and blocks its interaction with RANK | Denosumab (anti-RANK antibody; Prolia®; Xgeva®)                        | SC    | Bone metastasis (Xgeva)<br>Osteoporosis (Prolia)                                                                                                                                                                                                                                                                                                                                                                                                                             | Osteonecrosis of the jaw, hypocalcemia, hypophosphatemia, dyspnea, infusion-related reactions                                                                                                                                                                                          | For Xgeva, administer SC 120 mg every 4 weeks.<br>For Prolia, administer SC 60 mg every 6 months.<br>Monitor calcium levels.<br>Assess for and advise patients to report symptoms of osteonecrosis of the jaw or hypocalcemia. (Amgen, 2020b)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                                      | Mechanism of Action                              | Drug                                         | Route | Indications    | Side Effects                                                                                                                                                                                                                                                  | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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| Monoclonal antibodies:<br>Human<br>( <i>Cont.</i> ) | Binds to and prevents the ligand binding of EGFR | Necitumumab (anti-EGFR antibody; Portrazza®) | IV    | Squamous NSCLC | <p>Black box warning: in combination with gemcitabine and cisplatin, cardiopulmonary arrest or sudden death, hypomagnesemia</p> <p>Skin toxicity, rash, hypomagnesemia, hypocalcemia, hypophosphatemia, hypokalemia, vomiting, infusion-related reactions</p> | <p>Administer 800 mg IV infusion over 60 minutes on days 1 and 8 of each 21-day cycle. Administer IV infusion via a pump through a dedicated infusion line. Flush the line with normal saline injection, USP at the end of the infusion.</p> <p>Premedication with diphenhydramine is warranted in patients with one previous grade 1 or 2 infusion-related reaction.</p> <p>Premedication with diphenhydramine, acetaminophen, and dexamethasone is warranted in patients with a second infusion-related reaction.</p> <p>Adjust dose for adverse effects. Treatment may be held, adjusted, or discontinued based on the severity of toxicity.</p> <p>Monitor magnesium, calcium, and potassium prior to each infusion during treatment and at least 8 weeks following the completion of treatment.</p> <p>Advise patients to report symptoms of thromboembolic events.</p> <p>Advise patients to wear sunscreen and report dermatologic toxicities.</p> <p>Monitor for infusion reactions. Additional premedication may be warranted.</p> <p>This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring.<br/>(Eli Lilly and Company, 2015)</p> |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                                      | Mechanism of Action                                                                   | Drug                                      | Route | Indications                                                                                                                                                                                                                                                                                                                                                                          | Side Effects                                                                                                          | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
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| Monoclonal antibodies:<br>Human<br>( <i>Cont.</i> ) | Binds to the CD20 antigen on B cells, resulting in ADCC and complement-mediated lysis | Ofatumumab (anti-CD20 antibody; Arzerra®) | IV    | Previously untreated CLL, in combination with chlorambucil, in patients for whom fludarabine is inappropriate<br>Relapsed CLL, in combination with fludarabine and cyclophosphamide<br>Recurrent or progressive CLL, as extended treatment in patients with complete response or partial response after at least 2 lines of therapy<br>CLL refractory to fludarabine and alemtuzumab | Neutropenia, upper respiratory tract infections, pneumonia, infusion-related reactions, hepatitis B reactivation, TLS | For previously untreated CLL in combination with chlorambucil, administer a minimum of 3 cycles until best response or a maximum of 12 cycles as 300 mg on day 1 followed by 1,000 mg on day 8, then 1,000 mg on day 1 of subsequent 28-day cycles.<br>For relapsed CLL in combination with fludarabine and cyclophosphamide, administer a maximum of 6 cycles administered as 300 mg on day 1, followed by 1,000 mg on day 8, then 1,000 mg on day 1 of subsequent 28-day cycles.<br>Extended treatment in CLL <ul style="list-style-type: none"> <li>• Administer a maximum of 2 years as 300 mg on day 1 followed by 1,000 mg on day 8, then 1,000 mg 7 weeks later and every 8 weeks thereafter.</li> <li>• Administer 12 total doses as 300 mg initial dose, followed in 1 week by 2,000 mg weekly for 7 doses, followed 4 weeks later by 2,000 mg every 4 weeks.</li> <li>• Administer IV using an infusion pump, the provided in-line filter, and polyvinyl chloride administration sets.</li> </ul> Do not administer with other medications. Flush the line with normal saline, USP before and after each dose.<br>Begin infusion within 12 hours of preparation.<br>Follow the titration described in prescribing information.<br>Premedicate with acetaminophen, an IV or PO antihistamine, and an IV corticosteroid. Adjust dose for adverse effects. Treatment may be held or discontinued based on the severity of adverse effects.<br>Monitor hepatitis B serologies.<br>Monitor CBC and neurologic function.<br>Advise patients to report symptoms of myelosuppression.<br>(Novartis Pharmaceuticals, 2016) |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                                      | Mechanism of Action                               | Drug                                         | Route | Indications                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Side Effects                                                                                                                                                                                                                                                                                                                                                 | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
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| Monoclonal antibodies:<br>Human<br>( <i>Cont.</i> ) | Blocks the binding of ligands to EGFR             | Panitumumab (anti-EGFR antibody; Vectibix®)  | IV    | Metastatic wild-type <i>KRAS</i> colorectal cancer                                                                                                                                                                                                                                                                                                                                                                                                            | Black box warning: Dermatologic toxicities<br>Adverse effects: Fatigue, skin toxicity (acneiform dermatitis, pruritus, erythema, rash, exfoliation, paronychia, dry skin, fissures), ocular toxicity, nausea, diarrhea, vomiting, dyspnea, pulmonary fibrosis/ILD, infusion-related reactions                                                                | Administer 6 mg/kg as IV infusion every 14 days. If dose < 1,000 mg, infuse over 60 minutes. If dose > 1,000 mg, infuse over 90 minutes.<br>Do not administer as an IV push or bolus. Administer using a low-protein-binding 0.2-micron or 0.22-micron in-line filter. Refer to prescribing information for titration instructions.<br>Use the diluted solution within 6 hours of dilution if stored at room temperature. Adjust dose for adverse effects. Treatment may be held or discontinued based on the severity of adverse effects.<br>Monitor electrolytes, ocular toxicities (keratitis or ulcerative keratitis), and dermatologic toxicities.<br>Advise patients to limit sun exposure. This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring. (Amgen, 2015) |
|                                                     | Binds to VEGFR2 and prevents ligands from binding | Ramucirumab (anti-VEGFR2 antibody; Cyramza®) | IV    | Gastric or GEJ adenocarcinoma, as a single agent or in combination with paclitaxel, for advanced or metastatic disease that has progressed on or after prior fluoropyrimidine- or platinum-containing chemotherapy.<br>NSCLC<br>• In combination with docetaxel for metastatic disease with progression on or after platinum-based chemotherapy; progression of disease with EGFR or ALK genomic tumor aberrations on FDA-approved therapy prior to treatment | Hypertension, proteinuria, infusion-related reactions, impaired wound healing, risk of hemorrhage<br>Worsening of preexisting hepatic impairment, particularly hepatic encephalopathy, and hepatorenal syndrome for individuals with Child-Pugh A liver cirrhosis<br>See prescribing information for most common adverse reactions with combination therapy. | For gastric cancer, administer 8 mg/kg every 2 weeks as a single agent or in combination with weekly paclitaxel.<br>For NSCLC, administer 10 mg/kg on day 1 of a 21-day cycle prior to docetaxel.<br>For colorectal cancer, administer 8 mg/kg every 2 weeks prior to FOLFIRI.<br>For hepatocellular carcinoma, administer 8 mg/kg every 2 weeks.<br>Administer IV infusion over 60 minutes; schedule is specific to cancer type. Administer with normal saline only.<br>Administer with a protein-sparing 0.22-micron filter.<br>Premedicate with IV H <sub>1</sub> antagonist. If patients have had a prior grade 1 or 2 infusion-related reaction, also premedicate with dexamethasone and acetaminophen.                                                                                                                                                                                                       |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                                      | Mechanism of Action | Drug                                                          | Route | Indications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Side Effects | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
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| Monoclonal antibodies:<br>Human<br>( <i>Cont.</i> ) |                     | Ramucirumab (anti-VEGFR2 antibody; Cyramza®) ( <i>Cont.</i> ) |       | <ul style="list-style-type: none"> <li>In combination with erlotinib, as first-line treatment of metastatic disease with EGFR exon 19 deletions or exon 21 (L858R) variations</li> </ul> <p>Colorectal cancer, in combination with FOLFIRI, for disease progression on or after prior therapy with bevacizumab, oxaliplatin, and fluoropyrimidine</p> <p>Hepatocellular carcinoma, as a single agent, in patients who have an alpha fetoprotein <math>\geq 400</math> ng/ml and have been treated with sorafenib</p> |              | <p>Adjust dose for adverse effects. Treatment may be held or discontinued based on the severity of adverse effects.</p> <p>Monitor for infusion-related reactions, including severe and life-threatening reactions, primarily occurring during or following the first or second infusion. Assess for symptoms of infusion-related reactions, such as rigors/tremors, back pain/spasms, chest pain or tightness, chills, flushing, dyspnea, wheezing, hypoxia, and paresthesia. In severe cases, symptoms include bronchospasm, supraventricular tachycardia, and hypotension.</p> <p>Monitor blood pressure and discontinue if patients experience severe and uncontrolled hypertension. Withhold if hypertension is not medically controlled; resume once controlled. Discontinue for hypertensive crisis or hypertensive encephalopathy.</p> <p>Monitor urine protein levels and thyroid function.</p> <p>Discontinue in patients who develop wound healing complications that require medical intervention.</p> <p>Withhold drug 28 days prior to surgery and until the wound is healed.</p> <p>Monitor for signs and symptoms of bleeding and thrombosis.</p> <p>This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring.</p> <p>(Eli Lilly and Company, 2020)</p> |

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**TABLE 10-1.** Immunotherapy Agents (Continued)

| Classification                    | Mechanism of Action                                                                                                                  | Drug                   | Route | Indications | Side Effects                                                                                                                                                                                                                                  | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|------------------------|-------|-------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Monoclonal antibody:<br>Humanized | Targets CD52 antigen on B and T cells, monocytes, macrophages, and NK cells, resulting in antibody-dependent lysis of targeted cells | Alemtuzumab (Campath®) | IV    | B-cell CLL  | Black box warnings: bone marrow suppression, infusion-related reactions, infections<br>Headache, fatigue, rash, thyroid disease, nausea, lymphocytopenia, antibody development, infection, infusion-related reactions, nasopharyngitis, fever | Initiate at a dose of 3 mg daily IV over 2 hours. If tolerated, the dose can be escalated to 10 mg daily, then up to the maintenance dose of 30 mg IV.<br>The maintenance dose is administered 3 times per week for 12 weeks. Do not exceed doses of 30 mg per day or cumulative doses of 90 mg per week.<br>Do not administer as IV push or bolus.<br>Premedicate with an antihistamine and acetaminophen 30 minutes prior to the first dose, with dose escalations, and as clinically indicated.<br>Administer prophylaxis for <i>Pneumocystis jirovecii</i> pneumonia and herpes viruses; continue for at least 2 months after completion of therapy and until CD4 lymphocyte count is $\geq 200/\text{mm}^3$ .<br>Routinely monitor for CMV infection during treatment and at least 2 months after treatment. Withhold treatment for serious infections and during treatment for CMV infection or confirmed CMV viremia.<br>Monitor CBC and platelets.<br>Discontinue for autoimmune anemia or autoimmune thrombocytopenia.<br>Advise patients to report symptoms of infection or signs of thyroid disorder.<br>Advise patients not to be immunized with live viral vaccines if they have recently been treated.<br>This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring.<br>(Sanofi Genzyme, 2020) |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                                        | Mechanism of Action                                                            | Drug                                                                           | Route | Indications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|-------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Monoclonal antibody:<br>Humanized<br>( <i>Cont.</i> ) | Binds to VEGF and prevents binding with its receptors, inhibiting angiogenesis | Bevacizumab (Avastin®), bevacizumab-awwb (Mvasi®), bevacizumab-bvzr (Zirabev™) | IV    | Metastatic colorectal cancer, in combination with chemotherapy<br>Unresectable, locally advanced, recurrent, or metastatic nonsquamous NSCLC, in combination with chemotherapy<br>Recurrent glioblastoma in adults<br>Metastatic renal cell carcinoma, in combination with IFN alfa<br>Persistent, recurrent, or metastatic cervical cancer, in combination with chemotherapy<br>Stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal cancer, in combination chemotherapy following resection<br>Avastin only: Unresectable or metastatic hepatocellular carcinoma, in combination with atezolizumab | Hypertension, fatigue, pain, headache, abdominal pain, constipation, diarrhea, nausea, vomiting, loss of appetite, hyperglycemia, proteinuria, hemorrhage, leukopenia, upper respiratory tract infection, epistaxis, dyspnea, infusion-related reactions, rhinitis, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder, back pain, exfoliative dermatitis, GI perforations and fistula, surgery and wound healing complications, arterial thromboembolic events, venous thromboembolic events, posterior reversible encephalopathy syndrome, renal injury, congestive heart failure | Administer 5–10 mg/kg IV infusion every 2–3 weeks, depending on cancer type. Dosage and frequency are based on the indication. Monitor blood pressure and urine protein. Advise patients to use reliable contraception and report signs of thrombotic events and GI perforation. Diluted solution may be stored at 2°C–8°C for up to 8 hours. Do not administer as an IV push or bolus. Do not administer within 28 days before or after surgery and until the wound is fully healed. This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring. (Amgen, 2021b; Genentech, 2021b; Pfizer, 2021) |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                                        | Mechanism of Action                                                                                                                 | Drug                                    | Route | Indications                                                                                         | Side Effects                                                                                                         | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|-------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|-------|-----------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Monoclonal antibody:<br>Humanized<br>( <i>Cont.</i> ) | Binds to complement protein C5 to inhibit the formation of the terminal complement complex C5b-9 to mediate intravascular hemolysis | Eculizumab (anti-C5 antibody; Soliris®) | IV    | Hemolysis associated with paroxysmal nocturnal hemoglobinuria<br>Atypical hemolytic uremic syndrome | Headache, nasopharyngitis, back pain, nausea, increased risk of meningococcal infections, infusion-related reactions | For paroxysmal nocturnal hemoglobinuria, administer 600 mg IV over 35 minutes every 7 days for first 4 weeks, then 900 mg for the fifth dose 7 days later, then 900 mg every 14 days thereafter.<br>For atypical hemolytic uremic syndrome, administer 900 mg IV over 35 minutes every 7 days for first 4 weeks, then 1,200 mg for the fifth dose 7 days later, then 1,200 mg every 14 days thereafter. Monitor CBC and serum lactate dehydrogenase levels.<br>Administer by IV infusion over 35 minutes. If the infusion is slowed for infusion-related reactions, the total infusion time should not exceed 2 hours.<br>Do not use in patients with unresolved serious <i>Neisseria meningitidis</i> infection or those who are currently not vaccinated against it. Vaccinate patients at least 2 weeks in advance of the first dose of eculizumab. Revaccinate according to medical guidelines for vaccine use.<br>(Alexion Pharmaceuticals, 2020) |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                                        | Mechanism of Action                                                                                                                                                                                                            | Drug                            | Route | Indications                                                                                                                                                                                                                                                                                                  | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                                   | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|-------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Monoclonal antibody:<br>Humanized<br>( <i>Cont.</i> ) | Binds to SLAMF7, which is expressed on myeloma cells and NK cells; causes ADCC by binding to myeloma cells; when bound to NK cells, leads to immunostimulation of NK cells with increased NK cell-mediated anti-tumor activity | Elotuzumab (Empliciti®)         | IV    | Multiple myeloma, in combination with lenalidomide and dexamethasone, in patients who have received 1–3 prior therapies<br>Multiple myeloma, in combination with pomalidomide and dexamethasone, in patients who have received at least 2 prior therapies, including lenalidomide and a proteasome inhibitor | Bradycardia, tachycardia, altered blood pressure, fatigue, peripheral neuropathy, hyperglycemia, hypocalcemia, hypoalbuminemia, decreased serum bicarbonate, hyperkalemia, diarrhea, constipation, decreased appetite, lymphocytopenia, leukopenia, thrombocytopenia, increased serum alkaline phosphatase, infection, cough, nasopharyngitis, upper respiratory tract infection, pneumonia, fever, infusion-related reactions | Administer 10 mg/kg IV every week, with a 0.2- to 1.2-micron in-line filter, for the first 2 cycles, then every 2 weeks thereafter. Premedicate with an antihistamine PO or IV, an H <sub>2</sub> antagonist PO, acetaminophen 650–1,000 mg PO, and dexamethasone IV. Monitor liver function. Instruct patients to report symptoms of infection and signs of electrolyte imbalances. Complete infusion within 24 hours of reconstitution. Do not administer as an IV push or bolus. (Bristol-Myers Squibb, 2019)                                                                                                                                                                                                                                                                        |
|                                                       | CCR4-directed monoclonal antibody; targets CCR4 expressed on the surface of some T-cell malignancies and expressed on regulatory T cells and a subset of T helper type 2 cells                                                 | Mogamulizumab-kpkc (Poteligeo®) | IV    | Relapsed or refractory mycosis fungoides or Sézary syndrome in adults, after at least 1 prior systemic therapy                                                                                                                                                                                               | Dermatologic toxicity (e.g., rash, SJS, TEN), infusion-related reactions, fatigue, diarrhea, musculoskeletal pain, upper respiratory tract infection, autoimmune complications, hyperglycemia, anemia, thrombocytopenia, increased AST and ALT, neutropenia<br>Post-transplant complications of allogeneic HSCT, including graft-versus-host disease and transplant-related death                                              | Administer 1 mg/kg IV infusion over at least 60 minutes with an in-line 0.22-micron filter on days 1, 8, 15, and 22 of the first 28-day cycle and on days 1 and 15 of each subsequent cycle. Premedicate with diphenhydramine and acetaminophen for the first infusion. Do not coadminister with other drugs in the same IV line. Do not administer via SC or rapid IV. Some dosage forms contain polysorbate 80, which may cause delayed hypersensitivity reactions. Dose interruptions may be needed for severe infusion reactions or dermatologic toxicities. This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring. (Kyowa Kirin, 2018) |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                                        | Mechanism of Action                                                                                                       | Drug                       | Route | Indications                                                                                                                                                                                                                                                       | Side Effects                                                                                                                                                                                                                                                                                                                                                  | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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| Monoclonal antibody:<br>Humanized<br>( <i>Cont.</i> ) | Binds to ganglioside GD2 that is overexpressed on neuroblastoma cells; induces complement-dependent cytotoxicity and ADCC | Naxitamab-gqgk (Danyelza®) | IV    | Neuroblastoma, in combination with GM-CSF, in adult and pediatric patients aged > 1 year with relapsed or refractory high-risk disease in the bone or bone marrow that has demonstrated a partial response, minor response, or stable disease after prior therapy | Black box warnings: infusion-related reactions; neurotoxicity, including posterior leukoencephalopathy syndrome<br>Adverse effects: peripheral neuropathy, pain, infusion-related reactions, edema, fatigue, fever, cough, nausea, vomiting, diarrhea, headache, somnolence, neurologic eye disorders, infection, electrolyte abnormalities, myelosuppression | Administer 3 mg/kg/day on days 1, 3, and 5 of each cycle.<br>Repeat cycles every 4 weeks until complete response or partial response, then 5 additional cycles every 4 weeks.<br>Further cycles may be every 8 weeks.<br>Administer GM-CSF 250 mcg/m <sup>2</sup> /day as SC injection on days –4 to 0. Administer GM-CSF 500 mcg/m <sup>2</sup> /day as SC injection on days 1–5.<br>Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg up to 80 mg or equivalent) 30 minutes to 2 hours prior to infusion.<br>Administer an antihistamine, H <sub>2</sub> antagonist, acetaminophen, and antiemetic 30 minutes prior to infusion.<br>Administer the first cycle over 60 minutes. Subsequent cycles can be administered over 30–60 minutes, as tolerated.<br>Observe patients for a minimum of 2 hours following each infusion.<br>Administer naxitamab as an IV infusion only. GM-CSF should be administered at least 1 hour prior to naxitamab on days 1, 3, and 5 of a cycle.<br>Beginning 5 days prior to the first infusion, initiate a 12-day course of prophylactic medication for neuropathic pain (e.g., gabapentin).<br>Adjust dose for adverse effects. Treatment may be held, adjusted, or discontinued based on the severity of the adverse effects.<br>Monitor for infusion-related reactions.<br>Monitor for neurotoxicity, including peripheral neuropathy.<br>Monitor blood pressure before and during treatment.<br>This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring.<br>(Y-mAbs Therapeutics, 2020) |

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**TABLE 10-1.** Immunotherapy Agents (Continued)

| Classification                               | Mechanism of Action                                                                                     | Drug                   | Route | Indications                                                                                                                                                                                                                                                                                                                                                  | Side Effects                                                                                                                                                                                                                                                                                                                                                      | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
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| Monoclonal antibody:<br>Humanized<br>(Cont.) | Binds to CD20, expressed, on B cells; mediates immune-mediated tumor cell death by CDC, ADCC, and ADCP. | Obinutuzumab (Gazyva®) | IV    | <p>Previously untreated CLL, in combination with chlorambucil</p> <p>Follicular lymphoma</p> <ul style="list-style-type: none"> <li>Previously untreated stage II bulky, III, or IV disease, in combination with chemotherapy</li> <li>Relapsed disease or disease refractory to a rituximab-containing regimen, in combination with bendamustine</li> </ul> | <p>Black box warnings: hepatitis B reactivation, progressive multifocal leukoencephalopathy</p> <p>Adverse effects: hypophosphatemia, hypocalcemia, hyperkalemia, hyponatremia, hypoalbuminemia, lymphocytopenia, leukopenia, anemia, elevated LFTs, infection, decreased creatinine clearance, increased serum creatinine, cough, infusion-related reactions</p> | <p>For CLL, administer for six 28-day cycles:</p> <ul style="list-style-type: none"> <li>100 mg IV on day 1 of cycle 1</li> <li>900 mg on day 2 of cycle 1</li> <li>1,000 mg on days 8 and 15 of cycle 1</li> <li>1,000 mg on day 1 of cycles 2–6</li> </ul> <p>For follicular lymphoma, administer the following:</p> <ul style="list-style-type: none"> <li>1,000 mg on day 1, 8, and 15 of cycle 1</li> <li>1,000 mg on day 1 of cycles 2–6 or cycles 2–8</li> <li>Then 1,000 mg every 2 months for up to 2 years</li> </ul> <p>Administer as an IV infusion only. Do not mix with other medications. Premedicate with acetaminophen 650–1,000 mg, dexamethasone 20 mg IV, or methylprednisolone 80 mg IV and an antihistamine for cycle 1. For all subsequent infusions, premedicate with acetaminophen 650–1,000 mg.</p> <p>See prescribing information for titration guidelines.</p> <p>Adjust dose for adverse effects. Treatment may be held, adjusted, or discontinued based on the severity of the adverse effects.</p> <p>Monitor hepatitis B serologies, signs of TLS, CBC, and electrolytes.</p> <p>Patients should avoid live vaccines.</p> <p>Instruct patients to report symptoms of liver and kidney toxicities.</p> <p>This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring.</p> <p>(Genentech, 2021c)</p> |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                                        | Mechanism of Action                                                                                                                                                                                                                                                                                                               | Drug                                                      | Route | Indications                                                                                                                                                                                                                                                                                                                                                                      | Side Effects                                                                                                                                                                                                                                                                            | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|-------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Monoclonal antibody:<br>Humanized<br>( <i>Cont.</i> ) | Targets HER2 on breast cancer cells resulting in cell growth arrest and apoptosis; also causes ADCC                                                                                                                                                                                                                               | Pertuzumab (Perjeta®)                                     | IV    | HER2-positive breast cancer, in the neoadjuvant, adjuvant, or metastatic setting, in combination with trastuzumab and chemotherapy                                                                                                                                                                                                                                               | Black box warning: left ventricular dysfunction, embryo-fetal toxicity<br><br>Adverse effects: weakness, myalgias, neutropenia, anemia, diarrhea, nausea, vomiting, alopecia, rash, fatigue, headache, left ventricular cardiac dysfunction, infusion-related reactions                 | Administer the initial dose of 840 mg IV over 60 minutes.<br>Administer subsequent doses of 420 mg over 30–60 minutes.<br>Do not administer as an IV push or bolus.<br>Adjust dose for adverse effects. Treatment may be held or discontinued based on the severity of the adverse effects.<br>Monitor LVEF prior to and during therapy.<br>See prescribing information for schedule.<br>Monitor for infusion-related reactions.<br>This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring.<br>(Genentech, 2021e)                                                                                                                                                                                                                                                                     |
|                                                       | Pertuzumab and trastuzumab target HER2. Hyaluronidase (recombinant human) is an endoglycosidase used to increase the dispersion and absorption of SC coadministered drugs; it is a glycosylated single-chain protein produced by mammalian cells containing a DNA plasmid encoding for a soluble fragment of human hyaluronidase. | Pertuzumab, trastuzumab, and hyaluronidase-zzxf (Phesgo™) | SC    | Neoadjuvant treatment for HER2-positive locally advanced, inflammatory, or early-stage breast cancer<br>Neoadjuvant treatment for HER2-positive early-stage breast cancer at high risk for recurrence<br>HER2-positive metastatic breast cancer, in combination with docetaxel, in patients who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease | Black box warnings: cardiomyopathy, embryo-fetal toxicity, pulmonary toxicity<br><br>Adverse effects: alopecia, nausea, diarrhea, anemia, asthenia, neutropenia, fatigue, rash, peripheral neuropathy, pulmonary toxicity, cardiomyopathy, hypersensitivity, infusion-related reactions | The initial dose is 1,200 mg pertuzumab, 600 mg trastuzumab, and 30,000 units hyaluronidase SC over approximately 8 minutes into the thigh only.<br>Subsequent doses are 600 mg pertuzumab, 600 mg trastuzumab, and 20,000 units hyaluronidase SC over 5 minutes, administered every 3 weeks.<br>For SC administration, use in the thigh only. Do not administer via IV.<br>Adjust dose for adverse effects. Treatment may be held or discontinued based on the severity of the adverse effects.<br>Monitor for cardiac symptoms, including hypertension, arrhythmias, and left ventricular dysfunction.<br>Conduct a comprehensive cardiac assessment, including history, physical examination, and multigated acquisition scan, prior to beginning therapy, at regular intervals, and with cardiac symptoms.<br>Monitor for signs of pulmonary toxicity, including anaphylaxis, angioedema, interstitial pneumonitis, or ARDS. |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                                        | Mechanism of Action                                                                                                                                                                                                                | Drug                                                                          | Route | Indications                                                                                                                                                                                                       | Side Effects                                                                                                                                                          | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|-------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|-------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Monoclonal antibody:<br>Humanized<br>( <i>Cont.</i> ) |                                                                                                                                                                                                                                    | Pertuzumab, trastuzumab, and hyaluronidase-zzxf (Phesgo™)<br>( <i>Cont.</i> ) |       |                                                                                                                                                                                                                   |                                                                                                                                                                       | <p>Permanently discontinue in patients who experience anaphylaxis or severe hypersensitivity reactions.</p> <p>This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring.<br/>(Genentech, 2020b)</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                       | Binds to CD19 antigen expressed on the surface of pre-B and mature B cells and on several B-cell malignancies; on binding to CD19, mediates B-cell lysis through apoptosis and immune effector mechanisms, including ADCC and ADCP | Tafasitamab-cxix (Monjuvi®)                                                   | IV    | DLBCL, in combination with lenalidomide, in adults with relapsed or refractory disease not otherwise specified, including DLBCL arising from low-grade lymphoma, and those who are ineligible for autologous HSCT | Neutropenia, fatigue, anemia, diarrhea, thrombocytopenia, cough, fever, peripheral edema, respiratory tract infection, decreased appetite, infusion-related reactions | <p>Administer 12 mg/kg IV on the following days of a 28-day cycle:</p> <ul style="list-style-type: none"> <li>• Cycle 1: days 1, 4, 8, 15, and 22</li> <li>• Cycle 2 and 3: days 1, 8, 15, and 22</li> <li>• Cycle 4 and additional: days 1 and 15</li> </ul> <p>Administer as an IV infusion.</p> <p>Do not administer with other medications through the same line.</p> <p>Refer to prescribing information for titration.</p> <p>Premedicate with acetaminophen, H<sub>1</sub> antagonists, H<sub>2</sub> antagonists, and corticosteroids 30 minutes to 2 hours prior to infusion.</p> <p>Monitor patients frequently during the infusion for reactions.</p> <p>If patients do not experience infusion-related reactions during the first 3 infusions, premedication is optional for subsequent infusions.</p> <p>If patients experience an infusion-related reaction, administer premedication before each subsequent infusion.</p> <p>Monitor CBC. Growth factor support may be needed to treat myelosuppression.</p> <p>This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring.<br/>(MorphoSys, 2020)</p> |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                                        | Mechanism of Action                           | Drug                                                     | Route | Indications                                                                    | Side Effects                                                                                                                                                                                                                                                    | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|-------------------------------------------------------|-----------------------------------------------|----------------------------------------------------------|-------|--------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Monoclonal antibody:<br>Humanized<br>( <i>Cont.</i> ) | Targets HER2 on cancer cells, leading to ADCC | Trastuzumab (Herceptin®),<br>trastuzumab-pkrb (Herzuma®) | IV    | HER2-positive breast cancer<br>HER2-positive metastatic gastric and GEJ cancer | Black box warning: cardiomyopathy, infusion-related reactions, pulmonary toxicity, embryo-fetal toxicity<br><br>Decreased LVEF, pain, chills, headache, diarrhea, nausea, vomiting, abdominal pain, weakness, cough, dyspnea, fever, infusion-related reactions | For HER2-positive breast cancer in an adjuvant setting, administer an initial dose of 4 mg/kg IV, followed by 2 mg/kg IV weekly for 12–18 weeks. One week after the final weekly dose, administer 6 mg/kg IV every 3 weeks to complete 52 weeks of therapy.<br><br>Alternately, for HER2-positive breast cancer, the initial dose is 8 mg/kg IV, followed by 6 mg/kg IV every 3 weeks for 52 weeks.<br><br>For HER2-positive metastatic breast cancer, administer an initial dose of 4 mg/kg IV, followed by weekly doses of 2 mg/kg IV.<br><br>For HER2-positive metastatic gastric/GEJ cancer, administer an initial dose of 8 mg/kg IV, followed by 6 mg/kg IV every 3 weeks.<br><br>Administer as an IV infusion only<br>Adjust dose for adverse effects. Treatment may be held or discontinued based on the severity of the adverse effects.<br>Monitor LVEF prior to and during therapy.<br>Monitor for symptoms of cardiac failure and dysfunction.<br>Monitor for infusion-related reactions.<br>Monitor for pulmonary toxicity.<br>This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring.<br>(Genentech, 2021d; Teva Pharmaceuticals, 2019a) |

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**TABLE 10-1.** Immunotherapy Agents (Continued)

| Classification                         | Mechanism of Action                                                                                                                                                                                                                              | Drug                                                    | Route | Indications                                                                                                                                                                           | Side Effects                                                                                                                                                                                                                                                                                                                                                                    | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|----------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|-------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Monoclonal antibody: Humanized (Cont.) | Trastuzumab is a mediator of ADCC for HER2-overexpressing cancer cells. Hyaluronidase increases permeability of the SC tissue by depolymerizing hyaluronan and increases the absorption rate of a trastuzumab product into systemic circulation. | Trastuzumab and hyaluronidase-oysk (Herceptin Hylecta™) | SC    | HER2-positive breast cancer, as adjuvant therapy in combination with chemotherapy or as a single agent<br>HER2-positive metastatic breast cancer, in combination or as a single agent | Black box warnings: cardiomyopathy, pulmonary toxicity, embryo-fetal toxicity<br>Adverse effects: fatigue, arthralgia, diarrhea, injection site reaction, upper respiratory tract infection, rash, myalgia, nausea, headache, edema, flushing, fever, cough, extremity pain<br>May contribute to the exacerbation of chemotherapy-induced neutropenia and embryo-fetal toxicity | Administer trastuzumab 600 mg and hyaluronidase 10,000 units SC over 2–5 minutes once every 3 weeks.<br>If a dose is missed, administer the next dose as soon as possible, with the interval between doses < 3 weeks.<br>Administer SC only.<br>Alternate administration between left and right thigh, giving the injection at least 2.5 cm from the previous site and only to healthy skin without redness, bruising, tenderness, hardness, moles, or scars.<br>Adjust dose for adverse effects. Treatment may be held or discontinued based on the severity of the adverse effects.<br>Monitor for hypersensitivity and administration-related reactions, especially with the first dose.<br>Assess LVEF at baseline and every 3 months during treatment and at completion.<br>Refer to prescribing information for LVEF assessments.<br>Discontinue in the presence of cardiomyopathy, anaphylaxis, angioedema, interstitial pneumonitis, or ARDS.<br>This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring.<br>(Genentech, 2019) |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                                 | Mechanism of Action                                                                                                                                                                                                                                                                                                    | Drug                          | Route | Indications                                                                                                                                                                                       | Side Effects                                                                                                                                                                                                                                                                         | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|-------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Bispecific antibody                            | Binds to EGFR and MET receptor, disrupting EGFR and MET signaling functions through blockage and degradation of receptor; allows for targeting of tumor cells by immune effector cells, with NK cells causing ADCC and macrophages causing trogocytosis                                                                | Amivantamab-vmjw (Rybrevant®) | IV    | Locally advanced or metastatic NSCLC with EGFR exon 20 insertion variations that has progressed on or after platinum-based chemotherapy, in adults                                                | Infusion-related reactions, ILD/pneumonitis, acneiform dermatitis, TEN, ocular toxicity, embryo-fetal toxicity, rash, paronychia, musculoskeletal pain, dyspnea, nausea, vomiting, fatigue, edema, stomatitis, cough, constipation, decreased lymphocytes, hypokalemia, hyponatremia | Dose is based on baseline body weight: <ul style="list-style-type: none"> <li>• &lt; 80 kg: 1,050 mg</li> <li>• ≥ 80 kg: 1,400 mg</li> </ul> Premedicate with acetaminophen and antihistamine prior to all doses. Administer corticosteroid prior to initial doses on days 1 and 2 of week 1 of treatment. Infusion rates are dependent on dose, infusion schedule, and observed infusion-related reactions. See prescribing information for infusion rate table and adjustments for infusion reactions. Administer using 0.2-micron PES filter. Hold and discontinue therapy for presumed and confirmed ILD and severe dermatologic adverse events. This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring. (Janssen Biotech, 2021)                                                 |
| Bispecific T-cell engaging monoclonal antibody | Bispecific CD19-directed CD3 T-cell engager; binds to CD19 expressed on the surface of cells of B-lineage origin and CD3 expressed on the surface of T cells, which activates endogenous T cells by connecting CD3 in the T-cell receptor complex with CD19 on benign and malignant B cells; upregulates cell adhesion | Blinatumomab (Blinxyto®)      | IV    | CD19-positive B-cell precursor ALL in first or second complete response with MRD ≥ 0.1% in adults and children<br>CD19-positive relapsed or refractory B-cell precursor ALL in adults or children | Black box warning: CRS, neurotoxicity<br>Edema, hypertension, neurotoxicity, headache, rash, hypokalemia, nausea, vomiting, abdominal pain, anemia, thrombocytopenia, neutropenia, leukopenia, febrile neutropenia, elevated serum ALT, infection, fever, infusion-related reactions | For MRD-positive disease: <ul style="list-style-type: none"> <li>• Each treatment cycle consists of 4 weeks of continuous infusion followed by a 2-week treatment-free interval.</li> <li>• Therapy involves 1 induction cycle followed by up to 3 additional cycles for consolidation (a total of up to 4 cycles).</li> <li>• Administer 15 mcg/m<sup>2</sup>/day dose for weight &lt; 45 kg and flat dose 28 mcg/day for weight ≥ 45 kg.</li> <li>• Dosage is based on weight and cycle.</li> <li>• Premedicate with dexamethasone or prednisone 1 hour prior to the first dose of each cycle and if restarting after interruption of ≥ 4 hours in the first cycle.</li> </ul> For relapsed/refractory disease: <ul style="list-style-type: none"> <li>• The treatment course consists of up to 2 cycles for induction, followed by 3 additional cycles of consolidation, and up to 4 cycles of continued therapy.</li> </ul> |

(Continued on next page)

**TABLE 10-1.** Immunotherapy Agents *(Continued)*

| Classification                                                     | Mechanism of Action                                                                                                                                             | Drug                                         | Route | Indications | Side Effects | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|--------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|-------|-------------|--------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Bispecific T-cell engaging monoclonal antibody<br>( <i>Cont.</i> ) | molecules, production of cytolytic proteins, the release of inflammatory cytokines, and proliferation of T cells, which results in lysis of CD19-positive cells | Blinatumomab (Blincyto®)<br>( <i>Cont.</i> ) |       |             |              | <ul style="list-style-type: none"> <li>Dosing is based on weight and cycle, with an mcg/m<sup>2</sup>/day dose for weight &lt; 45 kg and a flat mcg/day dose for weight ≥ 45 kg.</li> <li>Premedicate with dexamethasone or prednisone 1 hour prior to the first dose of each cycle, prior to a step dose (such as cycle 1, day 8), and when restarting after interruption ≥ 4 hours.</li> </ul> <p>Administer as a continuous IV infusion for the daily dose; confirm infusion rate based on compounded infusion.</p> <p>Do not administer as an IV push or bolus. Instruct patients to refrain from driving while receiving blinatumomab infusion.</p> <p>Hospitalization is recommended for the first 9 days of the first cycle and the first 2 days of the second cycle.</p> <p>For MRD, hospitalization is recommended for the first 2 days of each cycle.</p> <p>Patients should be aware of the neurotoxicity effects and avoid activities that require mental alertness or coordination for the first dose. Instruct patients to report neurotoxicity, as well as symptoms of infection and pancreatitis.</p> <p>Advise patients not to change pump settings and to alert a healthcare worker immediately if the pump malfunctions.</p> <p>Do not flush the blinatumomab infusion line or IV catheter, especially when changing infusion bags. Flushing when changing bags or at the completion of the infusion can result in excess dosage and complications. Blinatumomab should be infused through a dedicated lumen of a vascular access catheter.</p> <p>CRS can occur and may be life-threatening or fatal. Interrupt or discontinue blinatumomab and treat with corticosteroids as recommended by the provider.</p> <p>(Amgen, 2021a)</p> |

(Continued on next page)

| Classification          | Mechanism of Action                                                                                                                 | Drug                                | Route                    | Indications                                                                                   | Side Effects                                                                                                                                                                                                               | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-------------------------|-------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|--------------------------|-----------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Oncolytic viral therapy | Replicates within tumors to produce the immune-stimulatory protein GM-CSF, causing tumor lysis and promoting an anti-tumor response | Talimogene laherparepvec (Imlygic®) | Intrale-sional injection | Unresectable cutaneous, SC, and nodal lesion melanoma that is recurrent after initial surgery | Immune-mediated events: glomerulo-nephritis, vasculitis, pneumonitis, worsen-ing psoriasis, vitiligo<br>Fever, fatigue, chills, nausea, vomiting, headache, flu-like symptoms, elevated liver enzymes, injection site pain | <p>Starting dose is up to a maximum of 4 ml at a concentration of 1 million PFU/ml.</p> <p>Subsequent doses should be up to 4 ml at a concentration of 100 million PFU/ml.</p> <p>Clean lesion and surrounding area with an alcohol swab and let dry.</p> <p>Administer topical or local anesthetic. Do not inject into the lesion.</p> <p>Inject talimogene laherparepvec into cutaneous, SC, or nodal lesions that are visible, palpable, or detectable by ultrasound guidance.</p> <p>Using a single insertion point, inject along multiple tracks as far as the radial reach of the needle to achieve complete dispersion.</p> <p>Multiple insertion points are permitted for larger lesions.</p> <p>Inject by pulling the needle back without exiting the lesion.</p> <p>If withdrawing, remove slowly to prevent leakage at the insertion point.</p> <p>Use a new needle each time the needle is completely removed from a lesion, and a different lesion is treated.</p> <p>Monitor the injection site for necrosis or ulceration, cellulitis, and infection.</p> <p>Keep injection site covered for at least 1 week after each treatment.</p> <p>Wear personal protective equipment when administering.</p> <p>Clean all surfaces that may have come into contact with the product using a virucidal agent.</p> <p>Immunocompromised individuals should <i>not</i> administer the drug, change dressings, or have contact with patient body fluids.</p> <p>Caregivers should wear protective gloves when assisting patients in applying or changing occlusive dressings.</p> <p>Dispose of dressings and cleaning materials used for the site in a sealed plastic bag and dispose of in household waste.</p> |

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**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                              | Mechanism of Action                                                                                                                             | Drug                                                       | Route | Indications                                                                                                                                                                                                                                                                                                                                                | Side Effects                                                                                                                                       | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|---------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------|-------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Oncolytic viral therapy<br>( <i>Cont.</i> ) |                                                                                                                                                 | Talimogene laherparepvec<br>(Imlygic®)<br>( <i>Cont.</i> ) |       |                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                    | This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring.<br>(Amgen, 2019; Hoffner et al., 2016)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Supportive care: Erythroid maturation agent | Binds to endogenous transforming growth factor-beta superfamily ligands, diminishing SMAD2/3 signaling to promote more effective erythropoiesis | Luspatercept-aamt<br>(Reblozyl®)                           | SC    | Transfusion-dependent beta-thalassemia in adults<br>Very low- to intermediate-risk myelodysplastic syndromes with ring sideroblasts or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis with anemia failing an erythropoiesis-stimulating agent and requiring 2 or more RBC transfusions over 8 weeks, in adults | Headache, bone pain, arthralgia, fatigue, cough, abdominal pain, diarrhea, dizziness<br><br>Risk for thrombosis, thromboembolism, and hypertension | For beta thalassemia, administer using the following schedule:<br><ul style="list-style-type: none"> <li>• Starting dose is 1 mg/kg once every 3 weeks.</li> <li>• Increase dose to 1.25 mg/kg every 3 weeks if there is no reduction in RBC transfusions after at least 2 consecutive doses at the starting dose.</li> <li>• Discontinue treatment if there is no reduction in RBC transfusions after at least 3 consecutive doses at the 1.25 mg/kg dose.</li> <li>• If predose Hgb is <math>\geq 11.5</math> g/dl and the Hgb level is not influenced by recent transfusion, delay dosing until Hgb is <math>\leq 11</math> g/dl.</li> <li>• Increases in Hgb greater than 2 g/dl within 3 weeks in the absence of transfusions will require a dose reduction based on the current dose.</li> </ul> For myelodysplastic syndromes, administer using the following schedule:<br><ul style="list-style-type: none"> <li>• Starting dose is 1 mg/kg once every 3 weeks.</li> <li>• Increase dose to 1.33 mg/kg every 3 weeks if patients are not RBC transfusion free after at least 2 consecutive doses at the starting dose.</li> <li>• Increase dose to 1.75 mg/kg every 3 weeks if patients are not RBC transfusion free after at least 2 consecutive doses at the 1.33 mg/kg dose.</li> <li>• Discontinue treatment if patients are not RBC transfusion free after at least 3 consecutive doses at the 1.75 mg/kg dose.</li> <li>• If predose Hgb is <math>\geq 11.5</math> g/dl and the Hgb level is not influenced by recent transfusion, delay dosing until Hgb is <math>\leq 11</math> g/dl.</li> </ul> |

(Continued on next page)



**TABLE 10-1.** Immunotherapy Agents (*Continued*)

| Classification                                                  | Mechanism of Action | Drug                                                | Route | Indications | Side Effects | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|-----------------------------------------------------------------|---------------------|-----------------------------------------------------|-------|-------------|--------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Supportive care: Erythroid maturation agent<br>( <i>Cont.</i> ) |                     | Luspatercept-aamt<br>(Reblozyl)<br>( <i>Cont.</i> ) |       |             |              | <ul style="list-style-type: none"> <li>Increases in Hgb greater than 2 g/d within 3 weeks in the absence of transfusions will require a dose reduction based on the current dose.</li> </ul> Administer SC into the upper arm, thigh, or abdomen.<br>If a planned administration is delayed or missed, administer as soon as possible, then continue dosing as prescribed, with at least 3 weeks between doses.<br>Adjust dose for adverse effects. <ul style="list-style-type: none"> <li>Discontinue treatment for grade 3–4 hypersensitivity reaction.</li> <li>For grade 3–4 adverse reactions, interrupt treatment until improvement to &lt; grade 1 and restart at the next lower dose.</li> </ul> Monitor blood pressure during therapy.<br>Antihypertensives should be used for new-onset or worsening hypertension.<br>The drug is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia.<br>This medication contains warnings for reproduction or lactation. Refer to the prescribing information for additional details on the risk and product-specific guidance in avoidance or monitoring.<br>(Celgene, 2019a) |

*Note.* Review package inserts for dosing and prescribing information.

ADCC—antibody-dependent cell-mediated cytotoxicity; ADCP—antibody-dependent cellular phagocytosis; ALK—anaplastic lymphoma kinase; ALL—acute lymphoblastic leukemia; ALT—alanine aminotransferase; AML—acute myeloid leukemia; ARDS—acute respiratory distress syndrome; AST—aspartate aminotransferase; BCMA—B-cell maturation antigen; CAR—chimeric antigen receptor; CBC—complete blood count; CCR4—C-C chemokine receptor type 4; CD—cluster of differentiation; CDC—complement-dependent cytotoxicity; cHL—classical Hodgkin lymphoma; CLL—chronic lymphocytic leukemia; CMV—cytomegalovirus; CRS—cytokine release syndrome; CYP—cytochrome P450; DLBCL—diffuse large B-cell lymphoma; dMMR—mismatch repair deficient; EGFR—epidermal growth factor receptor; Fc—fragment crystallizable; FDA—U.S. Food and Drug Administration; FOLFIRI—leucovorin, 5-fluorouracil, and irinotecan; 5-HT<sub>3</sub>—5-hydroxytryptamine-3; G-CSF—granulocyte-colony-stimulating factor; GEJ—gastroesophageal junction; GGT—gamma-glutamyltransferase; GI—gastrointestinal; GM-CSF—granulocyte macrophage-colony-stimulating factor; HER2—human epidermal growth factor receptor 2; Hgb—hemoglobin; HSCT—hematopoietic stem cell transplantation; IFN—interferon; Ig—immunoglobulin; IL—interleukin; ILD—interstitial lung disease; IM—intramuscular; IV—intravenous; LFTs—liver function tests; LVEF—left ventricular ejection fraction; MMAE—monomethyl auristatin E; MMAF—monomethyl auristatin F; MRD—minimal residual disease; MSI-H—microsatellite instability-high; NK—natural killer; NSCLC—non-small cell lung cancer; PAP—prostatic acid phosphatase; PD-L1/2—programmed cell death-ligand 1/2; PD-1—programmed cell death protein 1; PES—polyethersulfone; PFU—plaque-forming unit; PO—by mouth; RANK—receptor activator of nuclear factor kappa-B; RANKL—receptor activator of nuclear factor kappa-B ligand; RBC—red blood cell; REMS—risk evaluation and mitigation strategy; SC—subcutaneous; SCLC—small cell lung cancer; SJS—Stevens-Johnson Syndrome; SLAMF7—signaling lymphocytic activation molecule family member 7; TEN—toxic epidermal necrolysis; TLS—tumor lysis syndrome; Trop-2—trophoblast cell-surface antigen 2; UGT1A1—uridine diphosphate-glucuronosyl transferase 1A1; VEGF—vascular endothelial growth factor; ULN—upper limit of normal; USP—U.S. Pharmacopeia; VEGFR2—vascular endothelial growth factor receptor 2

e) Toxicities: Based on the mechanism of action, the most common toxicities associated with checkpoint inhibitors are immune-related adverse events (irAEs). These events are thought to be driven by an inflammatory response to immune-mediated activity, resulting in inflammation within one or more organ systems (Gordon et al., 2017; Postow et al., 2018; Villadolid & Amin, 2015). The extent of inflammation can range from mild to severe, and the onset of irAEs can range from immediately after treatment initiation to months after initiation (Thompson et al., 2019).

(1) Safe and effective management of irAEs necessitates a thorough baseline assessment and early recognition and may require supportive care and immunosuppressive agents. Patients and caregivers should be educated on irAEs, including signs and symptoms of toxicities, the importance of communication with the healthcare team, and management strategies.

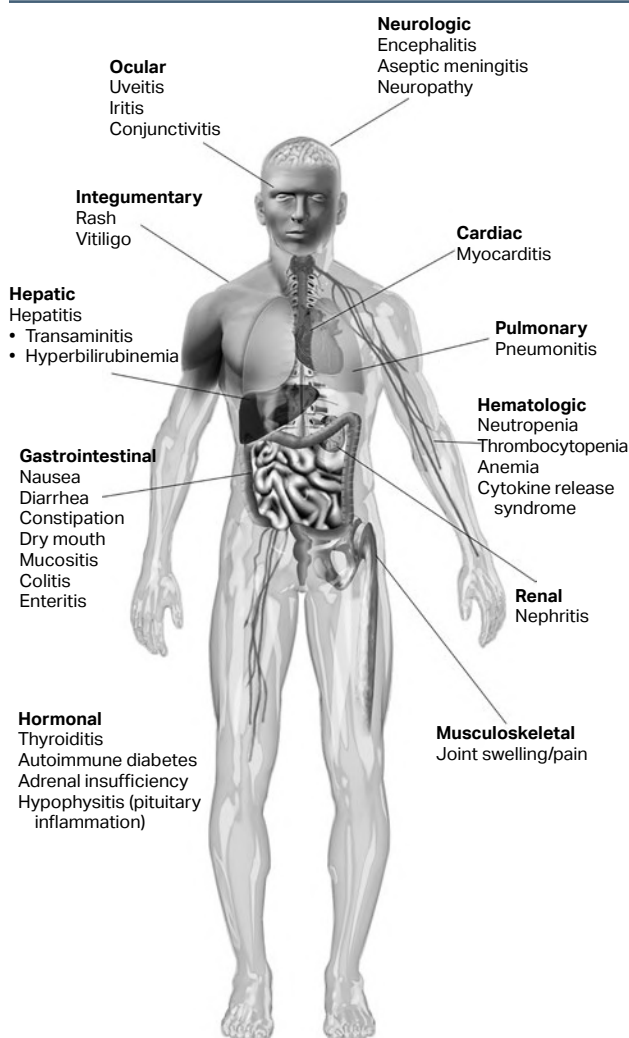
(2) Most commonly observed irAEs (see Figure 10-1)

- (a) Gastrointestinal (e.g., diarrhea, colitis)
- (b) Pulmonary (e.g., pneumonitis)
- (c) Dermatologic (e.g., rash, pruritus)
- (d) Endocrine (e.g., hypophysitis, hyperthyroidism, hypothyroidism)
- (e) Renal (e.g., nephritis)
- (f) Rheumatologic (e.g., arthralgias, myalgias)

(3) Several organizations, such as the American Society of Clinical Oncology, National Comprehensive Cancer Network (NCCN), Society for Immunotherapy of Cancer, and European Society for Medical Oncology, have published clinical guidelines for checkpoint inhibitor-related irAEs (Brahmer et al., 2018; Haanen et al., 2017; NCCN, 2022). General recommendations include the following (these may be different for specific manifestations of an irAE) (Brahmer et al., 2018):

- (a) Grade 1 toxicities can generally be managed with supportive care and close monitoring during immune checkpoint inhibitor therapy. An exception is made for certain irAEs, including neurologic and hematologic toxicities.
- (b) Grade 2 toxicities generally require holding immune checkpoint inhib-

**FIGURE 10-1.** Potential Side Effects and Toxicities of Immunotherapy by System



Note. Image courtesy of University of Texas MD Anderson Cancer Center. Used with permission.

itors until grade 1 or lower toxicity levels are achieved. Corticosteroids may be introduced for toxicity management. Of note, dose reduction of immune checkpoint inhibitors is not recommended.

- (c) Grade 3 toxicities require the immune checkpoint inhibitors to be held. High-dose corticosteroid therapy is recommended over six weeks. Response to the therapy determines the duration of corticosteroid or other immunosuppression. The decision to rechallenge with an immune checkpoint inhibitor after the resolution of a grade 3 irAE is an indi-

vidualized decision depending, in part, on the adverse event. Additional immunosuppression may be indicated with refractory symptoms. Referrals to organ-specific specialists should be considered for many irAEs.

(d) Grade 4 toxicities typically require permanent discontinuation of checkpoint inhibitors.

f) Education (Bayer et al., 2017)

- (1) Patients should be educated prior to and throughout therapy about the potential toxicities associated with immunotherapy.
- (2) Patients should be educated about the importance of contacting their care team, how to manage irAEs associated with therapy, and when to present to the hospital or emergency department for further assessment.

## 2. CAR T-cell immunotherapy

a) Pathophysiology

- (1) CAR T cells are genetically modified with a specific protein receptor that binds to a specific cancer antigen and causes cancer cell death.
- (2) This therapy uses CAR T cells with tumor-specific antigen recognition to target specific malignancies.
- (3) The T cells are generated through genetic modification of the patient's autologous T cells or from an allogeneic donor through leukapheresis (Ragoonanan et al., 2021). The cells are then expanded in a laboratory setting (Callahan et al., 2017).
- (4) Prior to the infusion of CAR T cells, patients will undergo lymphodepletion chemotherapy and subsequently have CAR T cells reinfused (Nair & Westin, 2020).
- (5) CAR T cells, through activation of T-cell memory, target malignant cells. This, along with the persistence of the CAR, allows for durable memory and improved relapse-free survival (June & Sadelain, 2018).

b) Mechanism of action

- (1) FDA-approved CAR T cells include tisagenlecleucel, axicabtagene ciloleucel, lisocabtagene maraleucel, idecabtagene vicleucel, and brexucabtagene autoleucel.
- (2) FDA initially approved four CAR T cells that target cluster of differentiation (CD)19 antigens present in most B-cell

leukemias and lymphomas. These include tisagenlecleucel, axicabtagene ciloleucel, lisocabtagene maraleucel, and brexucabtagene autoleucel (Sadelain et al., 2013).

- (3) FDA recently approved idecabtagene vicleucel, which targets B-cell maturation antigen (BCMA), for multiple myeloma (U.S. FDA, 2021).
- (4) All products currently on the market require a Risk Evaluation and Mitigation Strategy (REMS) from manufacturers to ensure the benefits outweigh the risks.

c) Indications

(1) Tisagenlecleucel

- (a) Approved for pediatric and young adult relapsed or refractory B-cell acute lymphoblastic leukemia
- (b) Patients up to age 25 years with B-cell precursor acute lymphoblastic leukemia that is refractory or in a second or later relapse
- (c) Adult relapsed or refractory diffuse large B-cell lymphoma (DLBCL) or relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma
- (d) Excludes primary central nervous system lymphoma (Novartis Pharmaceuticals, 2021)

(2) Axicabtagene ciloleucel

- (a) Adults with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma
- (b) Excludes primary central nervous system lymphoma (Kite Pharma, 2021b)
- (c) Adults with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy (Kite Pharma, 2021b)

(3) Lisocabtagene maraleucel

- (a) Adults with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL, DLBCL arising from indolent lymphoma, high-grade B-cell lymphoma, primary medi-

- astinal large B-cell lymphoma, and follicular lymphoma grade 3B (Bristol-Myers Squibb, 2021)
- (b) Excludes primary central nervous system lymphoma (Bristol-Myers Squibb, 2021)
- (4) Idecabtagene vicleucel: adults with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody (Celgene, 2021a)
- (5) Brexucabtagene autoleucel
  - (a) Adults with relapsed or refractory mantle cell lymphoma
  - (b) This product received accelerated approval based on its response rate. Continued approval is dependent on confirmatory trial results (Kite Pharma, 2021a).
- d) Collaborative management
  - (1) Administration
    - (a) Emergency equipment, including a code cart and hypersensitivity kit, should be available during CAR T-cell infusion.
    - (b) Neurotoxicity is a common toxicity of CAR T-cell therapy. It is important to have a baseline neurologic examination and ensure patients are on seizure prophylaxis medication (Neelapu et al., 2019).
    - (c) Central venous access is recommended for IV administration of current CAR T-cell therapies.
    - (d) Nursing care includes administration of fluids and premedications as ordered, careful assessment for signs and symptoms of infusion reactions, and documentation of the specific product administered in the medical record (Halton et al., 2017).
  - (2) Monitoring
    - (a) Monitoring after the cell infusion is important for the early identification of any toxicities.
    - (b) Vital signs should be monitored minimally every four hours and more frequently based on clinical assessment.
    - (c) Changes in clinical status and symptoms, such as pain, infection, neurologic changes, laboratory inflammatory biomarkers and coagulopathies, and organ toxicities, should be monitored following the infusion and as clinically necessary.
  - (d) Monitoring fluid status may include daily weights, intake and output, and symptoms of edema. Neurologic assessments should occur every shift and more often if any changes are noted.
  - (e) Daily review of laboratory results, organ systems, neurologic assessments, and physical examination should be performed.
- (3) Assessment
  - (a) Early recognition of changes could lead to earlier intervention for more severe side effects, such as cerebral edema and severe cytokine release syndrome (CRS).
  - (b) Bedside nurses are in key positions for assessment, as they will likely be the first to recognize any changes and can promptly notify the oncology provider for further management.
- (4) Follow-up
  - (a) Patients will need routine follow-up with an oncology provider for several weeks after infusion to assess the onset of toxicities, hematologic recovery, and overall health.
  - (b) Follow-up of disease status may include bone marrow aspirate, biopsies, and radiologic imaging appropriate for the disease.
  - (c) Patients who received CAR T-cell therapy in a clinical trial may be asked to participate in long-term follow-up to monitor the persistence of the CAR T cells, adverse events, disease relapse, or other autoimmune or hematologic disorders (McConville et al., 2017).
- e) Toxicities
  - (1) Intensive monitoring, accurate grading, and prompt management of toxicities with aggressive supportive care have reduced the morbidity and mortality associated with CAR T-cell therapy (Neelapu et al., 2019).
  - (2) The location for toxicity management is determined by the severity of toxicity, the status of the patient, and the resources available at the treatment site. Some care may require more intensive monitoring. An intensive care unit may be considered

for those with severe toxicities who need a higher level of care.

- (3) Other toxicities seen with CAR T cells include tumor lysis syndrome, cytopenias, and sequelae such as infections, which are medically managed per standard of care.
- (4) A grading system is important for managing toxicities. Since the approval of the first CAR T-cell therapies, many grading systems have been used for symptoms like CRS. The American Society for Transplantation and Cell Therapy published a consensus grading tool to assess the severity and management of CRS, organ toxicity, and neurotoxicity (D.W. Lee et al., 2019).
- (5) CRS
  - (a) CRS is a common toxicity of CAR T-cell therapy. The hallmark of CRS is elevated inflammatory cytokines caused by immune system activation, with patients demonstrating dramatic increases in the cytokine interleukin (IL)-6 levels following CAR T-cell infusion.
  - (b) CRS symptoms include myalgias, headaches, fever, fatigue, nausea, hypotension, and capillary leak.
  - (c) Supportive care only can be considered for mild CRS management. Moderate to severe cases require the addition of corticosteroids, tocilizumab, and standard medical management for constitutional symptoms.
  - (d) CRS may have a delayed onset, rarely beyond 14 days, and should be carefully evaluated for other causes outside this window (D.W. Lee et al., 2019).
  - (e) Tocilizumab is approved for the treatment and management of severe CRS. The administration of tocilizumab, an IL-6 inhibitor, leads to an almost immediate reversal of CRS (Bonifant et al., 2016).
    - i. The tocilizumab dose is weight based.
    - ii. The recommended dose for patients who weigh less than 30 kg is a 12 mg/kg IV infusion over 60 minutes. The dose is 8 mg/kg in patients who weigh 30 kg or more.
    - iii. Depending on CRS severity, some patients may require

repeat dosing. The interval between consecutive doses should be at least eight hours apart with a maximum 800 mg IV infusion (Genentech, 2021a).

- (6) Immune effector cell-associated neurotoxicity syndrome (ICANS)
  - (a) Mild to potentially fatal neurotoxicity is associated with CAR T-cell therapy. Neurologic assessment is imperative.
  - (b) The immune cell-associated encephalopathy (ICE) score and the American Society for Transplantation and Cellular Therapy ICANS consensus grading for children or adults aids in determining the severity and management of neurotoxicity (D.W. Lee et al., 2019).
  - (c) Neurotoxicity hallmark signs are confusion, aphasia, and seizures.
- (7) Hemophagocytic lymphohistiocytosis/macrophage-activation syndrome (HLH/MAS)
  - (a) HLH/MAS is a life-threatening hyperinflammatory syndrome with high mortality that can occur after CAR T-cell therapy.
  - (b) It can be difficult to diagnose in the context of CRS, as both are on the spectrum of systemic hyperinflammatory disorders. New criteria for diagnosing HLH/MAS after CAR T-cell therapy are needed, as non-specific traditional diagnostic criteria are also used for CRS diagnosis.
  - (c) The occurrence of HLH/MAS requires additional management, as it does not respond to the corticosteroids or tocilizumab strategies used for CRS. Therefore, if no improvement is seen after 48 hours, etoposide treatment or intrathecal cytarabine for neurotoxicity must be considered (Neelapu et al., 2019).
- (8) B-cell aplasia
  - (a) B-cell aplasia is the mass death of B cells.
  - (b) CD19 and BCMA are expressed in healthy B cells responsible for producing antibodies that kill pathogens. These healthy B cells are also killed by infused CAR T cells that target CD19 and BCMA antigens. Patients must subsequently receive

immunoglobulin therapy to fight off infections (Maude et al., 2015; Wang et al., 2021).

*f) Education*

- (1) Nurses should initiate patient education prior to CAR T-cell therapy.
- (2) Important topics include caregiver requirements, financial implications, infection prevention, and emergency management.
- (3) Written and verbal education should be provided to patients and caregivers about the treatment, signs and symptoms of toxicities, toxicity management, and the importance of prompt reporting of toxicities to the oncology provider. Education should be provided and documented prior to and throughout treatment (Halton et al., 2017).
- (4) Patients should be educated about adherence to long-term follow-up once discharged from direct patient care. Patients enrolled in clinical trials may be asked to participate in long-term follow-up to monitor for the persistence of the CAR T cells, adverse events, disease relapse, or other autoimmune or hematologic disorders (e.g., B-cell aplasia) (McConville et al., 2017).

**3. Cytokines**

*a) Pathophysiology:* Cytokines are small protein molecules released by different cells throughout the body, aiding with communication between the cells of the immune system via stimulator or suppressor signals (S. Lee & Margolin, 2011; Silk & Margolin, 2019).

- (1) They can be further classified based on the proximity of the signaling cell to the target cell (Owen et al., 2013).
  - (a) Endocrine action requires the cytokine to transmit its signal via the blood circulation to its distant target.
  - (b) Paracrine action is when the cytokine signal must diffuse through tissue fluids across an immunologic synapse.
  - (c) Autocrine action is when a cell receives a signal from a cytokine within its membrane receptors.
- (2) Cytokines generally are activated by a stimulus and induce responses by binding to specific receptors (Owen et al., 2013).
  - (a) Cells expressing receptors for specific cytokines can be activated or inhibited,

altering the immune effector function.

(b) Some cytokines are pleiotropic. They can induce different outcomes based on the nature of the target cell.

*b) Mechanism of action* (S. Lee & Margolin, 2011; Owen et al., 2013)

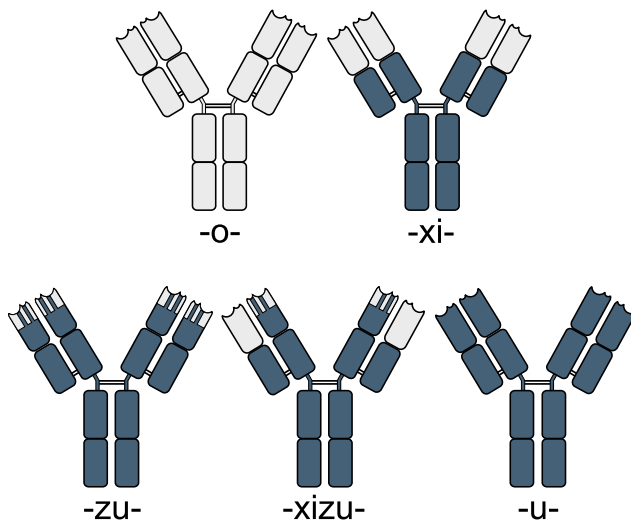
- (1) Cytokines affect the growth, differentiation, and function of white blood cells, red blood cells, platelets, and other cells that regulate immune and inflammatory responses within the body.
  - (2) Cytokines may enhance the cytotoxic activity of the cells of the immune system and secrete additional cytokines, resulting in amplification or suppression of the immune response.
    - (a) An enhanced immune response may include proliferation or activation and recruitment of additional immune effector cells.
    - (b) This is also known as the cascade effect, in which one cytokine reaches its receptor on the target cell, and then that cell produces one or more additional cytokines.
  - (3) Select cytokines can exact proinflammatory, anti-inflammatory, and regulatory functions in the immune system, such as hematopoiesis and wound healing.
  - (4) Select cytokines can send signals that inhibit or promote cell death.
  - (5) Select cytokines include a variety of chemokines—a small group of cytokines that help mobilize immune cells toward specific sites in the body.
  - (6) Cytokines regulate antibody production, the functions of B and T cells, and interactions with antigen-presenting cells and natural killer cells.
- c) Indications:* Cytokines have diverse indications based on categories grouped as follows (Becker et al., 2020):
- (1) Hematopoietic growth factors
    - (a) Hematopoietic growth factors stimulate growth, differentiation, and maturation of target cells.
    - (b) The stimulating growth factors commonly used in patients with cancer are isolated to stimulate red blood cells, platelets, and white blood cells. Table 10-1 lists current FDA-approved drugs. Examples include epoetin alfa and filgrastim (Baldo, 2016).



- (c) Biosimilars have been FDA approved for some growth factors. They have no clinically meaningful difference from the reference product. Biosimilars will have the same amino acid sequence, but “differences can be seen in the 3-dimensional structure, glycosylation site, isoform profiles, and the level of protein aggregation” (Becker et al., 2020, p. 15). Biosimilar use is regulated by FDA approval but may be determined by factors in a practice site or payer.
- (2) Interferons (IFNs) (Parker et al., 2016)
  - (a) IFNs are currently used as anti-neoplastic and antiviral therapies. This chapter focuses on the current FDA-approved antitumor treatments.
  - (b) IFN is part of the cell’s defense mechanism against viruses and other foreign substances. It was discovered in the 1950s when scientists saw that it interfered with viral replication and growth.
  - (c) IFN inhibits B-lymphocyte (B-cell) activation, enhances T-lymphocyte (T-cell) activity, and increases the cellular destruction capability of natural killer cells.
  - (d) Three forms of IFNs exist—alpha, beta, and gamma. IFN alpha and beta can be produced by any cell exposed to the virus, whereas IFN gamma is only secreted by natural killer cells and T lymphocytes (Owen et al., 2013). Examples include IFN alfa-2b, peginterferon alfa-2b (alpha), IFN beta, and IFN gamma.
- (3) ILs
  - (a) ILs are naturally occurring proteins secreted by cells in response to a stimulus, such as an infection. Once ILs are bound to a receptor, a cascade effect is created of signals that regulate the growth, differentiation, and motility of cells (Ardolino et al., 2015).
  - (b) ILs were discovered in the 1970s and named as such because it appeared they were made by leukocytes and acted on other leukocytes. Further discoveries revealed they are created by many different cells and provide a variety of functions (Owen et al., 2013).
  - (c) Currently, 40 known ILs exist, and each functions differently with receptors on various cells (Justiz-Vaillant & Qurie, 2021). Examples include aldesleukin (IL-2) and oprelvekin (IL-11).
  - (4) Current research is exploring the combined therapy of cytokines with other immunotherapies, such as immune checkpoint inhibitors, but none are FDA approved. The current FDA-approved cytokines for cancer therapy are IFN alfa and IL-2 (Rahimi Kalateh Shah Moham-mad et al., 2020; Runbeck et al., 2021).
- d) Collaborative management
  - (1) Administration: Cytokines have diverse administration routes.
  - (2) Monitoring
    - (a) IFNs: Monitor laboratory values, specifically white blood cells, hemoglobin, platelets, and kidney and liver function. Assess for injection site redness versus infection or cellulitis.
    - (b) ILs: Monitor laboratory values, including complete blood count and kidney and liver function (Clinigen, 2019).
- e) Toxicities: Cytokine toxicities vary by agent.
- f) Education
  - (1) Patients might be reluctant to discuss side effects because they are concerned about dose reductions or delays. Ask specific questions related to drug therapy so that management can occur quickly and appropriately.
  - (2) Educate patients and caregivers to report new symptoms to their provider immediately.
    - (a) IFNs: Nausea, vomiting, loss of appetite, weight loss, hair loss, dry skin/rash, and fatigue are anticipated side effects. Notify providers of any depression and suicidal thoughts or plans. Avoid alcohol use (Merck, 2015, 2019).
    - (b) ILs: Possible side effects include diarrhea, worsening rash with or without itching, cough, shortness of breath, swelling of the extremities, chest pain, tachycardia, yellowing of the skin and eyes, bloated feeling, abdominal distension, loss of appetite, and headache (Clinigen, 2019).
      - i. Use unscented, dye-free creams to help with the rash.

- ii. Document weight daily while on therapy and notify the healthcare team of a 10% loss or gain.
  - (3) Be aware that some immunotherapy, especially agents that stimulate cytokines, can cause ongoing overstimulation of the immune system. These side effects might require lifelong management.
  - (4) Counsel patients to avoid getting pregnant during all therapies. Include information on reliable contraception methods, such as intrauterine devices, oral contraceptive pills, condoms, and spermicide.
- 4. Immunomodulators
  - a) Pathophysiology
    - (1) Immunomodulators are a class of agents used to modify immune response activity. These agents may have antiangiogenic or antineoplastic properties.
    - (2) Immunomodulators are used in various diseases, including Crohn disease and cancers, and primarily target pathways related to multiple myeloma (e.g., thalidomide). *IMiD* is a common term to describe the immunomodulatory drugs used to treat myeloma.
  - b) Mechanism of action
    - (1) IMiDs
      - (a) Cereblon, a human protein encoded by the *CRBN* gene, has recently been identified as the primary target for this class of agents, where binding to *CRBN* occurs. The breakdown of transcription factors IKZF1 and IKZF3 occurs, resulting in the upregulation of IL-2 expression in T cells (Asatsuma-Okumura et al., 2019). Examples include pomalidomide and thalidomide.
      - (b) Additionally, CK1a degradation results in effective cell death mediated by the action of *TP53* (Asatsuma-Okumura et al., 2019). An example includes lenalidomide.
    - (2) Topical immunomodulatory agents: Modulation of monocytes, macrophages, and dendritic cells occurs with some immunomodulators that act on natural killer cells, T cells, and B cells (Mahatma et al., 2020). An example includes imiquimod.
  - c) Indications
    - (1) Indications for immunomodulators include primarily hematologic malignancies.
    - (2) Other indications include topical use to manage skin conditions, such as basal cell carcinoma, when patients are poor surgical candidates (e.g., imiquimod).
  - d) Collaborative management
    - (1) Administration: Routes include oral and topical administration. This class of agents is highly teratogenic when given orally; therefore, safe handling by providers, patients, and caregivers is essential.
    - (2) Monitoring: Prior to therapy, pregnancy screening (two tests) in women of child-bearing potential is imperative.
  - e) Toxicities: Reproductive toxicities, nerve damage, myelosuppression, and blood clots can occur. Patients can experience flu-like symptoms while taking IMiDs.
  - f) Education: Appropriate contraception should be used up to four weeks before and after treatment.
- 5. Monoclonal antibodies (mAbs)
  - a) Pathophysiology
    - (1) The mAbs are highly specific antibodies produced by a clone of a single hybridoma cell. They are produced in living cells and are laboratory substances.
    - (2) An antigen-specific plasma cell is produced and fused with a cancerous immune cell for immortality. This is followed by the cell being cloned to produce numerous daughter clones that continuously produce the desired mAb.
    - (3) The mAbs can restore, enhance, or mimic the immune system's ability to attack cancer cells (Rhyman & Meibohm, 2017). The currently marketed immune checkpoint inhibitors are mAbs.
    - (4) The mAbs bind with proteins and antigens.
    - (5) Classification by source (see Figure 10-2)
      - (a) Murine means made from mice (suffix: *-omab*). An example includes blinatumomab.
      - (b) Chimeric means part mouse and part human (suffix: *-ximab*). Examples include brentuximab, cetuximab, and rituximab.
      - (c) Humanized means small portions of mouse antibodies are attached to human antibodies (suffix: *-zumab*). Examples include emtansine, alemtuzumab, bevacizumab, elotuzumab, gemtuzumab, ozogamicin, obinutuzumab, pertuzumab, and trastuzumab.
      - (d) Human means completely human antibodies (suffix: *-umab*). Examples



**FIGURE 10-2.** Types of Monoclonal Antibodies

Comparison of monoclonal antibodies (dark—human, light—nonhuman):

- Top row: mouse, chimeric
- Bottom row: humanized, chimeric/humanized, human

The subtypes according to the nomenclature of monoclonal antibodies are shown below each antibody.

Note. From "Chimeric and Humanized Antibodies," by Anypodetos, 2010. Retrieved from [https://en.wikipedia.org/wiki/File:Chimeric\\_and\\_humanized\\_antibodies.svg#file](https://en.wikipedia.org/wiki/File:Chimeric_and_humanized_antibodies.svg#file). This work has been released into the public domain by its author, Anypodetos at English Wikipedia. Anypodetos grants anyone the right to use this work for any purpose, without any conditions, unless such conditions are required by law.

include daratumumab, denosumab, necitumumab, ofatumumab, panitumumab, and ramucirumab.

- (6) Classifications may be determined by the mAb target. Examples include CD20-targeted, SLAMF7-targeted, HER2-targeted, CD38-targeted, IL-6-targeted, PD-1-targeted, and CD5-targeted agents.

*b) Mechanism of action*

- (1) The mAbs can function in several manners (Bayer, 2019).

*(a) Direct tumor cell death*

- This method involves the mAbs ability to bind to cancer cells that contain tumor antigens. The antigens then prompt apoptosis (unconjugated antibodies).
- The mAbs also can bind to a receptor, blocking any antigens that would fuel cancer growth (unconjugated antibodies).

*(b) Cell death by immune mediation*

- This method involves the immune system seeking out cancer cells and destroying them.
- This is prompted by several mechanisms that can include phagocytosis, inhibition of T-cell inhibitory receptors, and complement activation.

(c) Antibodies can be conjugated to an element toxic to cancer cells (e.g., chemotherapy, radiation, another toxin). These antibodies can then be used to destroy tumor cells (conjugated antibodies). Examples include ado-trastuzumab and enfortumab vedotin.

- (2) Unconjugated antibodies (American Cancer Society, 2019)

(a) Unconjugated antibodies are the most common mAbs available in the United States used for cancer treatment.

(b) The antibodies function by themselves, whereas conjugated antibodies join with a drug or particle.

(c) Unconjugated antibodies work by binding to cancer cells and mimicking a marker so that the immune system will destroy it. An example is alemtuzumab, which can be used to treat chronic lymphocytic leukemia. This mAb binds to CD52 antigens on hematopoietic cells, thus drawing the immune cells to destroy them.

(d) Other mAbs can work by blocking the antigens on cancer cells that can help cancer spread. An example is trastuzumab, which can be used to treat HER2-positive breast cancer. This mAb binds to the HER2 protein, impairing its functionality.

- (3) Antibody-drug conjugates (Criscitiello et al., 2021)

(a) These conjugates work by merging the selectivity of mAbs with the cell-killing properties of chemotherapy. Antibodies incorporated are mainly humanized antibodies.

(b) These conjugates directly transport cytotoxic drug into the tumor space, thus transforming chemotherapy into a targeted agent.

(c) Examples include trastuzumab deruxtecan (targeting HER2), sacituzumabgovitecan (targeting Trop2),

and enfortumab vedotin (targeting Nectin4).

(4) Conjugated antibodies (American Cancer Society, 2019)

(a) The antibodies work by combining with a chemotherapy agent or radioactive particle.

- i. The mAbs deliver the conjugated agent straight to cancer cells in the body. An example is ado-trastuzumab emtansine, which can be used to treat breast cancer. It is attached to DM1, a microtubule inhibitor, and targets the HER2 protein.
- ii. The mAbs attach directly to cancer cell surface antigens so that the conjugated agent can be directly delivered.
- iii. Similar to trastuzumab, ado-trastuzumab emtansine inhibits HER2 receptor signaling.

(b) Targeted radionuclide therapy and radioimmunotherapy

- i. Pathophysiology: Radiolabeled antibodies have small radioactive particles attached to a mAb. The mAb and radiation are delivered directly to the target cells because the mAb attaches to the target while the radiation affects the target and nearby cells to a certain extent (American Cancer Society, 2019).
  - $^{90}\text{Y}$ -Ibritumomab tiuxetan is an antibody against the CD20 antigen bound to yttrium-90. The antibody delivers radioactivity directly to cancer cells and is made of a mAb (ibritumomab) and radioactive substance (yttrium-90) (American Cancer Society, 2019).
  - Radioimmunotherapy is a form of targeted radionuclide therapy that uses mAbs conjugated to therapeutic radionuclides.
  - This is an attempt to augment the single-agent efficacy by conjugating thera-

peutic radionuclides to the mAbs to optimize radiation delivery to the tumor while minimizing total body exposure to radiation (Sachpedkidis et al., 2019).

ii. Mechanism of action (Sachpedkidis et al., 2019)

- The action involves a combination of the antibody-stimulated cytotoxicity and induction of apoptosis.
- Ionizing radiation emitted from the radioisotope leads to free radicals and subsequent cellular damage.
- Adjacent tumor cells that do not bind to the antibody may still be killed through the radiation crossfire effect.

iii. Targeted radionuclide therapy with external beam radiation therapy (Gill et al., 2017)

- Synergy arises because external beam radiation therapy acts locally on the primary tumor, whereas the targeted radionuclide therapy can also target beyond the radiation field.
- Another interaction between these two methods is the effect of radiation therapy on blood flow and vessel permeability, leading to enhanced intratumor accumulation of the targets radionuclides as a result of the vasculature perturbation after the radiation therapy takes place.

(5) Bispecific mAbs (American Cancer Society, 2019).

(a) Bispecific mAbs comprise two different mAbs attaching to two different proteins simultaneously. By binding to both protein targets, the drugs bring the cancer cells and immune cells together, causing the immune system to attack the cancer cell.

(b) Blinatumomab is an example of a bispecific engager used to treat some types of leukemia. One part attaches to the CD19 protein, and another attaches to CD3.

c) Indications: Indications for mAbs include solid tumor and hematologic malignancies. These agents are used alone and in combination with other anticancer therapies.

- (1) Radioimmunotherapy is administered to treat hematologic tumors.
- (2) The mAbs are used in various diseases beyond cancer.

d) Collaborative management

- (1) The mAb administration is determined by the drug product. Some mAbs are given via IV infusion, and others are given subcutaneously.

(a) Some agents have been tested for safety as treatment during pregnancy and may have the potential for harm during fetal development. Treatment in pregnant women should be determined by the agent and clinical situation (Sarno et al., 2013).

(b) Radioimmunotherapy is administered on a specific regimen, including pretargeting tissues with an unconjugated mAb (e.g., rituximab) followed by the radiolabeled isotope. Pretargeting is a strategy to decrease toxicity to healthy tissue while enhancing the radiation dose to the tumor. This is achieved by separating the tumor antigen targeting phase from the radioisotope delivery phase (Patra et al., 2016).

i.  $^{90}\text{Y}$ -ibritumomab tiuxetan can safely be administered in the outpatient setting with few discharge instructions and minimal risk of radiation exposure to others.

ii. Because the primary route of elimination for  $^{90}\text{Y}$ -ibritumomab tiuxetan is through the kidneys, urine and other body fluids should be flushed down the toilet and any spills cleaned up. Linens contaminated with body fluids should be washed separately. Handwashing should be emphasized.

- (2) Monitoring for radioimmunotherapy

(a) Complete blood count, urinalysis, thyroid function testing, pregnancy testing, and cardiovascular and pulmonary assessment are rec-

ommended prior to therapy (Gharwan & Groninger, 2016).

(b) Monitor for acute infusion reactions.

(c) Monitor for acute and long-term system-related toxicities, including cardiac, renal, and dermatologic toxicities; myelosuppression; and thromboembolic events (Gharwan & Groninger, 2016).

e) Toxicities

(1) CRS can be accompanied by nausea, headache, fever, rash, tachycardia, and dyspnea. More severe side effects can include hypotension, seizures, and psychotic symptoms (Posner et al., 2019).

(2) Common side effects include allergic-type reactions (e.g., hives, pruritus) and flu-like symptoms (e.g., fatigue, headache, muscle ache, chills, fever, nausea, vomiting, diarrhea) (Gharwan & Groninger, 2016).

(3) Hypersensitivity reactions can include rash, fever, urticaria, and angioedema (Posner et al., 2019).

(4) Fully human mAbs are considered less immunogenic than humanized or chimeric mAbs. However, even fully human proteins can elicit an unwanted immune response (Picard & Galvão, 2017).

(5) Allergic reactions with murine mAbs are common when used in humans and often result in the induction of antidrug antibodies (Bayer, 2019).

(6) Almost all patients with an immediate reaction can be safely reexposed through desensitization or challenge, depending on the severity of the initial reaction (Picard & Galvão, 2017).

(7) Toxicities are also related to the specific target.

f) Education

(1) Patients should use precautions to prevent pregnancy during and following treatment according to drug-specific recommendations.

(2) Additional education should be provided based on the specific mAb being administered.

g) Radioimmunotherapy-specific considerations

(1) Administration

(a) As with many oncologic therapies, radioimmunotherapy involves an interprofessional and coordinated approach to achieve the desired patient outcomes.

- (b) Radiation safety precautions will depend on the specific isotope used.
    - (c) For clinicians, safety precautions include standard universal precautions with the addition of acrylic shielding during administration.
    - (d) For safe and effective use of radioimmunotherapy, accurate dose planning should be emphasized (Evans-Axelsson et al., 2016).
  - (2) Monitoring: Monitor for any signs of infusion or allergic reaction, such as urticaria, respiratory or cardiac abnormalities, and any symptoms of extravasation during the infusion.
  - (3) Education
    - (a) Additional education should be provided based on the specific therapies being administered.
    - (b) The ability to generate an immune response to any vaccine following the <sup>90</sup>Y-ibritumomab tiuxetan regimen has not been studied. Additionally, live viral vaccines should not be administered to patients who have recently received <sup>90</sup>Y-ibritumomab tiuxetan (Acrotech Biopharma, 2019).
    - (c) Females of reproductive potential and males with female partners of reproductive potential should use effective contraception during treatment and for a minimum of 12 months after the final dose. Fetal harm can occur, as can harm through lactation (Acrotech Biopharma, 2019).
6. Oncolytic viral therapies
- a) Pathophysiology: Oncolytic viral immunotherapy is a viral-targeted therapy that directly kills cancer cells by causing tumor death and producing tumor-toxic cytokines or antitumor host immune responses. The two oncolytic viral immunotherapies are nonpathogenic (harmless to humans) and pathogenic (requiring genetic modification for use) (Abd-Aziz & Poh, 2021; Prestwich et al., 2008).
  - b) Mechanism of action
    - (1) The only FDA-approved agent is talimogene laherparepvec (Andtbacka et al., 2015).
    - (2) The two primary processes by which oncolytic viruses destroy cancer is direct cell lysis and induction of antitumor immunity (Goradel et al., 2021). The four mechanisms of action thought to exist with oncolytic viral immunotherapies include the following (Abd-Aziz & Poh, 2021; Goradel et al., 2021; Wollmann et al., 2012):
      - (a) Viral cell receptor responses target viral-specific cell surface receptors overexpressed in cancer cells.
      - (b) Cytokine release is seen with double-stranded RNA viruses that cause antiviral cellular activation of cytokines that promote apoptosis (e.g., influenza).
      - (c) Nuclear replication of cancer cells can be disrupted by certain double-stranded DNA viruses that have been genetically modified to target tumor DNA synthesis.
      - (d) Innate immune response is activated by introducing specific synergistic viruses to kill cancer cells. Tumor lysis subsequently aids in the release of tumor-associated antigens.
  - c) Indications: Oncolytic viral immunotherapies, including adenoviruses, poliovirus, coxsackievirus, herpes simplex virus 1, measles virus, Newcastle disease virus, reovirus, vaccinia virus, and vesicular stomatitis virus, are being investigated in clinical trials across a wide array of cancer types (Abd-Aziz & Poh, 2021; Eager & Nemunaitis, 2011; Msaouel et al., 2013). However, the only FDA-approved indication for use at the time of this publication is the genetically modified herpes simplex virus 1 to treat metastatic melanoma (Andtbacka et al., 2015).
  - d) Collaborative management
    - (1) Administration: intralesional injection for metastatic melanoma
      - (a) Safe handling (Hoffner et al., 2016)
        - i. Change the needle after each injection to avoid infection.
        - ii. Apply sterile gauze to the site for at least 30 seconds after injection.
        - iii. Discard gloves immediately after injection and perform hand hygiene. After donning a new set of gloves, apply an absorbent pad and dry occlusive dressing to the site. Wipe the surface of the occlusive dressing with an alcohol swab to remove any surface virus that has shed.

- (b) Immunocompromised and pregnant individuals (e.g., caregivers) should not handle, administer, or care for the injection site of the drug (Amgen, 2019).
  - (2) Monitoring: Monitor for injection site pain, redness, infection, and irritation.
  - e) Toxicities: Fever, malaise, chills, nausea, vomiting, headache, elevated liver enzymes, injection site pain, and autoimmune vitiligo are toxicities.
  - f) Education
    - (1) Patients should be in contact isolation for seven days. This is important if they have subsequent visits to a clinic or a planned procedure (Amgen, 2019).
    - (2) Counsel patients and caregivers on using standard precautions when changing dressings, including safe disposal (placing soiled dressings in a sealed bag).
    - (3) To prevent possible viral infections, counsel patients on avoiding young children, pregnant women, and immunocompromised individuals during treatment (Amgen, 2019).
- C. General patient and family education
1. Convey to patients and families that immunotherapy is not chemotherapy and works differently within the body (Brahmer et al., 2018).
  2. Inform patients and families that some immunotherapies, such as immune checkpoint inhibitors, have an immune response that may continue after drug discontinuation (Brahmer et al., 2018).
  3. Instruct patients to inform their provider of any new medications or dietary supplements introduced during therapy (Bayer et al., 2017).
  4. Educate patients about side effects and potential toxicities unique to immunotherapies (Bayer et al., 2017).
  5. Educate patients on the importance of communication with the healthcare team and when to seek medical management (e.g., hospital or emergency department for toxicity management) (Bayer et al., 2017).
  6. Encourage patients to carry a card to identify the type of immunotherapy they receive. This can be useful when presenting for care in an emergency department, clinic, or another primary provider outside the cancer care setting (Brahmer et al., 2018; see Figure 10-3).
  7. Educate patients and caregivers about the importance of follow-up to monitor late-term effects, as the healthcare community has yet to know the long-term effects of newer therapies (Buitrago et al., 2019).

**FIGURE 10-3.** Wallet Card for Patients Receiving Immunotherapy

## IMMUNOTHERAPY

WALLET CARD

NAME: \_\_\_\_\_

CANCER DX: \_\_\_\_\_

I-O AGENTS RCVD: ☐ CHECKPOINT INHIBITOR(S)

☐ CAR-T ☐ VACCINES ☐ ONCOLYTIC VIRAL THERAPY

☐ MONOCLONAL ANTIBODIES

DRUG NAME(S): \_\_\_\_\_

IMMUNOTHERAPY TX START DATE: \_\_\_\_\_

OTHER CANCER MEDICATIONS: \_\_\_\_\_

NOTE: IMMUNOTHERAPY AGENTS ARE **NOT** CHEMOTHERAPY AND SIDE EFFECTS MUST BE MANAGED DIFFERENTLY (SEE BACK)

## IMMUNOTHERAPY

CARD

IMMUNE-RELATED SIDE EFFECTS\*, COMMON WITH CHECKPOINT INHIBITORS VARY IN SEVERITY AND MAY REQUIRE REFERRAL AND STEROIDS. PATIENTS HAVE A LIFETIME RISK OF IMMUNE-RELATED SIDE EFFECTS.

\*MAY PRESENT AS RASH, DIARRHEA, ABDOMINAL PAIN, COUGH, FATIGUE, HEADACHES, VISION CHANGES, ETC.—CONFERR WITH ONCOLOGY TEAM BEFORE CHANGING I-O REGIMEN OR STARTING SIDE EFFECT TREATMENT.

ONCOLOGY PROVIDER NAME \_\_\_\_\_

ONCOLOGY PROVIDER NO. \_\_\_\_\_

EMERGENCY CONTACT \_\_\_\_\_

CONTACT PHONE NO. \_\_\_\_\_

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Note. Copyright 2018 by Oncology Nursing Society. Used with permission. For more information and to order cards, visit [https://www.ons.org/sites/default/files/2019-01/IO%20Card%201-sided\\_Vertical.pdf](https://www.ons.org/sites/default/files/2019-01/IO%20Card%201-sided_Vertical.pdf).

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## SECTION IV

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# Treatment Administration and Safety

Chapter 11. Administration Considerations

Chapter 12. Safe Handling of Hazardous Drugs

Chapter 13. Infusion-Related Complications



## CHAPTER 11

# Administration Considerations

### A. Components of safe and effective administration of cancer therapies

1. Comprehensive pretreatment assessment
2. System safeguards to prevent errors and manage emergencies
3. Dose calculations and verification processes
4. Evidence-based practices for all routes of chemotherapy, targeted therapy, and immunotherapy administration
5. Refer to Chapter 1 for nursing scope and standards, professional education, policy and procedure requirements, and an overview of antineoplastic medication safety. Chapter 12 reviews safe handling precautions for hazardous drugs (HDs). Chapter 13 discusses infiltration, extravasation, and infusion-related complications.

### B. Pretreatment

1. A thorough assessment of the patient, patient history, and cancer treatment plan, including orders and treatment notes, with proactive interventions can prevent adverse reactions and errors.
  - a) The assessment should be performed for all routes of chemotherapy, targeted therapy, and immunotherapy, including those given orally.
  - b) Assess information specific to the agent (see Tables 6-1, 7-1, 8-1, and 10-1) and route of administration.
  - c) Identify questions and concerns that require discussion or collaboration with the patient's provider.
2. Before the administration of a new treatment regimen, review the patient's medical record for the following elements (Neuss et al., 2016):
  - a) Cancer diagnosis, stage, and current cancer status (e.g., progression)
  - b) Cancer treatment plan, including goals of therapy, medications, and duration of treatment
    - (1) Goals include chemoprevention, cure, control, or palliation. Electronic documentation systems often have a location for the

prescriber to document goals on the treatment plan. Some informed consent documents include goals of treatment.

- (a) Compare the goals of therapy documented with the patient's understanding.
    - (b) Discuss discrepancies with the provider.
  - (2) For curative therapy, the duration of treatment is often a set number of cycles. However, for metastatic disease, treatment may continue until disease progression, unacceptable toxicity, or the decision to decline or terminate treatment.
- c) Planned frequency of office visits and patient monitoring appropriate for the treatment plan
  - (1) The National Comprehensive Cancer Network (NCCN, [www.nccn.org](http://www.nccn.org)) has disease-specific guidelines and chemotherapy order templates that include suggested patient monitoring for cancer type and stage (e.g., type and timing of imaging) and treatment regimen.
  - (2) See Appendix C for an example of a chemotherapy order template.
- d) Allergies, risk, and history of infusion-related reactions (see Chapter 13)
  - (1) Risk factors for hypersensitivity reactions include multiple allergies, cardiovascular disease, asthma, older age, and previous exposure to the agent (Shaker et al., 2020).
  - (2) Patients are at the highest risk for infusion-related reactions and cytokine release syndrome at the initiation of the first dose of monoclonal antibodies. Patients with B-cell lymphomas and leukemias with high circulating blast counts (greater than 25,000/mm<sup>3</sup>) or who have bulky disease are at increased risk for reactions with the initiation of treatment with

- anti-cluster of differentiation 20 (CD20) antibodies (e.g., rituximab) (Genentech, 2021b).
- (3) Review the grade (severity), symptoms, onset, course of progression, interventions, patient response, and time to resolution of symptoms for past infusion-related reactions. A thorough history is an essential risk assessment tool when administering chemotherapy or immunotherapy (Andrews, 2017).
    - (a) Documentation tools and grading systems should be integrated into electronic health records to identify patients who have had reactions (Andrews, 2017; see Chapter 13).
    - (b) For many agents, the grade of the previous reaction is used to order future premedications, infusion rates, and infusion volumes. It is also used to determine if patients can receive medication over a shorter period in the future or via the subcutaneous (SC) route (Genentech, 2021b, 2021c).
    - (c) Previous reactions may require a change in treatment location for future treatments (inpatient vs. outpatient), desensitization protocols, and an increased nurse-to-patient ratio.
  - (4) Verify that emergency equipment and supplies are available, not expired, functional, and that staff are aware of their location. Ensure that treatment chairs can change to the supine position if needed and that oxygen tanks are not empty.
- e) Risk factors for adverse reactions related to disease and treatment history
- (1) Patients with rapidly growing cancers, such as small cell lung cancer, aggressive forms of lymphoma, and acute leukemia, have an increased risk for tumor lysis syndrome at the initiation of treatment (NCCN, 2021a, 2021b, 2021f, 2022a).
  - (2) Hematologic malignancy or bone marrow involvement increases the risk for myelosuppression from chemotherapy (NCCN, 2021a, 2022a).
  - (3) A patient's cancer treatment history can contribute to toxicities for the planned therapy.
    - (a) Radiation recall, characterized by an acute inflammatory reaction confined to previously irradiated sites, can be triggered by the administration of some agents (e.g., doxorubicin) and can occur months to years after radiation (I.C. Liu et al., 2020).
    - (b) Prior treatment with an anthracycline antitumor antibiotic can increase the risk of congestive heart failure if other cardiotoxic therapies are planned (Polonsky & DeCara, 2019). Review cumulative doses of all drugs in this category. See Table 6-1 for cumulative dose information for each anthracycline drug and Chapter 16 for information on cardiotoxicity.
    - (c) Concurrent chemotherapy and radiation therapy can increase toxicity. For example, concurrent therapy for non-small cell lung cancer increases the risk and severity of esophagitis versus radiation therapy alone (Or et al., 2021).
- f) Comorbidities and noncancer treatments
- (1) Comorbidities and treatments should be assessed for potential adverse effects on patient outcomes.
  - (2) Comorbidity index scoring systems capture complexity and assign a score (Charlson et al., 1987; Wass et al., 2016). Multiple comorbidities can negatively affect cancer therapies and patient outcomes (Sarfati et al., 2016).
  - (3) Comorbidities that can affect cancer therapies include the following:
    - (a) Congestive heart failure
      - i. Congestive heart failure can preclude treatment with anthracycline antitumor antibiotics and HER2 receptor antibodies (NCCN, 2021g).
      - ii. Patients with congestive heart failure are at risk for fluid overload with hydration that is often needed to prevent nephrotoxicity from cisplatin or hemorrhagic cystitis from cyclophosphamide and ifosfamide.
    - (b) Diabetes
      - i. Poor glycemic control in patients with cancer has been associated with neutropenia, infections, and mortality (Arreskov et al., 2019; Storey et al., 2021).
      - ii. Blood glucose can be more challenging to control in patients receiving steroids as

part of a chemotherapy treatment plan, as steroids can increase blood glucose (Hershey & Hession, 2017; see Figure 22-1).

- iii. Patients with complications from diabetes have been found to have more than twice the risk for chemotherapy-related neuropathy (Hershman et al., 2016).

(c) Liver disease

- i. Liver disease can alter hepatic drug metabolism and cause high or prolonged drug levels with increased toxicity and worsening liver function (Kasi et al., 2015).
- ii. All patients should be asked if they have a personal history of hepatitis B (Hwang et al., 2020).
- iii. Patients who are hepatitis B positive and receiving chemotherapy or immunotherapy are at an increased risk for hepatitis B reactivation at the initiation of treatment (Hwang et al., 2020).

(d) Renal failure

- i. Many chemotherapies, targeted therapies, and immunotherapy agents are excreted primarily by the kidneys. Impaired renal function can lead to alterations in pharmacokinetics, elevated blood levels of drugs, and increased toxicity (Krens et al., 2019).
- ii. Hemodialysis can remove some chemotherapy and immunotherapy agents from the blood.
- iii. Collaboration with a nephrologist, oncologist, and pharmacist can determine if dose adjustments are needed and the appropriate timing to avoid drug removal from dialysis.

(e) Plasmapheresis

- i. Patients with cancer sometimes require plasmapheresis for hyperviscosity syndrome and leukocytosis.
- ii. Plasmapheresis can remove some medications from the

plasma, lowering serum concentration and affecting therapeutic levels.

- iii. Typically, drugs with high plasma protein binding affinity (greater than 80%) and low volumes of distribution (less than 0.2 L/kg) remain in the intravascular compartment and are most vulnerable to influences from plasmapheresis (Chen et al., 2017).

g) Medications

- (1) Review the patient's current medications.
- (2) Verify that the patient has been prescribed supportive medications.
- (3) Verify that the patient understands the purpose, dosing, administration instructions, and schedule of all medications.
  - (a) Provide the patient with written and verbal information and a calendar (as appropriate).

(b) Examples of supportive medications

- i. Antibiotics, antifungals, and antiviral agents: NCCN (2021e) has published guidelines for infection prophylaxis for various regimens based on the risk for infection.
- ii. Antidiarrheal agents: Patients receiving capecitabine, 5-fluorouracil, irinotecan, and other agents with an increased risk for diarrhea should be prescribed antidiarrheal agents such as loperamide (Krishnamurthi & Macaron, 2021).
- iii. Antiemetics

- Several studies have indicated that adherence to post-chemotherapy antiemetics, especially dexamethasone, is low and results in an increased incidence of nausea and vomiting (Mellin et al., 2018).
- Patient education has improved adherence and decreased the incidence of nausea and vomiting (Hendricks, 2015; Mellin et al., 2018).
- Clear communication between patients and nurses as to when the patient took

- prechemotherapy oral antiemetics is imperative to ensure that the antiemetics have time to take effect before infusions are initiated.
- iv. High-dose methotrexate
    - Administration of oral agents such as sodium bicarbonate and acetazolamide before patient admission for high-dose methotrexate successfully increases urine pH and prevents renal toxicity (Clemmons et al., 2021; Kramer et al., 2021).
    - Administration of oral medications before hospitalization can decrease the length of hospital stay by allowing earlier administration of methotrexate (Clemmons et al., 2021; Kramer et al., 2021).
    - Oral administration allows treatment when parenteral shortages of sodium bicarbonate occur.
    - Oral administration of agents to increase urine pH facilitates outpatient administration of high-dose methotrexate (NCCN, 2020).
- (4) Drug interactions: Assess for antineoplastic drug–drug interactions and food–drug interactions. Online resources such as Lexicomp provide details on these interactions (<https://online.lexi.com/lco/action/login>; login required). Examples of potential interactions include the following (Parsad & Ratain, 2017):
- (a) CYP3A4 inhibitors and inducers: Some antineoplastic agents are metabolized through the cytochrome P450 enzymes in the liver, especially CYP3A4. Many medications and herbs can inhibit or induce this enzyme and affect drug levels.
    - i. CYP3A4 inducers decrease the level of the drug, making it less effective.
    - ii. CYP3A4 inhibitors increase the concentration of the drug and contribute to increased toxicities.
    - iii. Strong CYP3A4 inducers and inhibitors should be avoided in patients if that pathway metabolizes the antineoplastic agent. When avoidance is not possible, some medications have specific dosing recommendations that should be followed.
    - iv. A significant interaction can occur when antineoplastic agents that are CYP3A4 inhibitors are used with opioids that are also CYP3A4 inhibitors (e.g., fentanyl) (Janssen Biotech, 2021). Fatal overdoses of fentanyl have been reported. This also can occur when antineoplastic agents that are CYP3A4 inducers are discontinued.
  - (b) QT-prolonging medications: Prolonged QT intervals can place patients at risk for life-threatening ventricular arrhythmias such as torsades de pointes. Risk is increased in patients receiving more than one QT-prolonging agent and those with an underlying prolonged QT or an electrolyte imbalance (Duan et al., 2018).
    - i. Examples of antineoplastic agents that can prolong QT intervals include arsenic trioxide, capecitabine, crizotinib, dasatinib, eribulin, dasatinib, lapatinib, and sunitinib (Duan et al., 2018).
    - ii. Significant nonantineoplastic medications that can prolong QT intervals include antipsychotics, 5-hydroxytryptamine-3 (5-HT<sub>3</sub>) antagonist antiemetics, antibiotics, antifungals, and antiarrhythmics (Farzam & Tivakaran, 2021).
    - iii. Methadone, an analgesic frequently used in cancer, can also prolong QT intervals (Farzam & Tivakaran, 2021).
  - (c) Nephrotoxic medications: Nonsteroidal anti-inflammatory drugs can potentiate renal toxicity in patients receiving nephrotoxic chemotherapy (e.g., cisplatin) (Sato et

- al., 2016). Caution should be used when administering nonsteroidal anti-inflammatory drugs to patients with mild to moderate renal insufficiency receiving pemetrexed (Eli Lilly and Company, 2017).
- (d) Steroids and immunotherapy: Poorer outcomes were reported in patients who received corticosteroids of greater than 10 mg of prednisone equivalent per day with an immune checkpoint inhibitor. Adverse effects on overall survival were not recorded when steroids were used for symptom control during treatment with immune checkpoint inhibitors. (Petrelli et al., 2020). Collaboration with the oncologist, pharmacist, and rheumatologist (if indicated) should occur to determine a plan for patients requiring steroids for comorbidities such as autoimmune diseases.
- h) Immunizations: Before initiating therapy, assess patient immunization status.
- (1) Patients with hematologic and solid tumor malignancies should receive the inactivated influenza virus vaccine annually (Centers for Disease Control and Prevention, 2022; Rubin et al., 2014).
  - (2) Inactivated vaccines can be administered safely to people with altered immunocompetence (Centers for Disease Control and Prevention, 2022; Rubin et al., 2014).
  - (3) Live vaccines should be avoided (Centers for Disease Control and Prevention, 2022; Rubin et al., 2014). If a patient recently received a live virus, contact the provider.
  - (4) Vaccination recommendations should be reviewed thoroughly, as instructions change frequently.
  - (5) Except for the inactivated influenza vaccine, vaccination during chemotherapy or radiation therapy should be delayed, if possible, because antibody response might be suboptimal (Centers for Disease Control and Prevention, 2022; Rubin et al., 2014).
  - (6) Information for COVID-19 vaccine and patients receiving antineoplastics (NCCN, 2022e):
    - (a) Immunization is recommended for all eligible patients, including patients with cancer undergoing treatment and cancer survivors six months of age and older, based on U.S. Food and Drug Administration–approved indications or emergency use authorization (EUA).
    - (b) To maximize vaccine efficacy, the vaccination should be delayed for at least three months following hematopoietic cell transplantation or engineered cellular therapy (e.g., chimeric antigen receptor T-cell therapy).
    - (c) For patients with hematologic cancers receiving intensive chemotherapy (e.g., cytarabine- or anthracycline-based induction regimens for acute myeloid leukemia), vaccination should be delayed until absolute neutrophil count recovery.
    - (d) For patients with solid tumor malignancies undergoing major surgery, separate the date of surgery from the vaccination by at least a few days.
    - (e) Caregivers, household members, and close contacts should be immunized.
    - (f) The NCCN committee prefers the use of mRNA vaccines for the primary series and boosters.
- i) Complementary and alternative therapies: Review the use of complementary and alternative therapies and assess for any interactions with planned treatment. See the Office of Cancer Complementary and Alternative Medicine website for more information (<https://cam.cancer.gov>).
- (1) Alternative care refers to nontraditional treatment interventions used in place of conventional medicine. Although there may be anecdotal evidence addressing the benefits, this care has not been subjected to the type of rigorous testing for safety and efficacy.
  - (2) Complementary health approaches refer to diverse medical and healthcare systems, practices, and products used with conventional medicine or usual care. They are not used as an alternative or in place of conventional medicine unless as part of a clinical trial.
  - (3) Examples include natural products (e.g., herbs/botanicals, vitamins, minerals), essential oils (e.g., aromatherapy), and mind–body practices (e.g., acupuncture, acupressure, chiropractic and osteopathic manipulation, healing touch, hypnotherapy, massage, meditation, movement therapies). The Office of Cancer Complementary and Alternative Medicine provides a

helpful workbook to help patients talk to healthcare providers about complementary and alternative medicine ([https://cam.cancer.gov/health\\_information/talking\\_about\\_cam.htm](https://cam.cancer.gov/health_information/talking_about_cam.htm))

- (4) Potential interactions and adverse reactions to herbs, vitamins, minerals, and other supplements should be monitored.

j) Age

- (1) The patient's age should be recorded to determine potential issues associated with various age groups.
- (2) Challenges regarding dosing for older patients include inadequate representation in oncology clinical trials, higher risk of treatment-related toxicity, increased risk of drug interactions with multiple medications, and physiologic effects of the natural aging process (e.g., decreased bone marrow reserves) (Lichtman et al., 2016; Parikh, 2018).

(a) Many chemotherapy toxicity prediction tools for older adults are available on the American Society of Clinical Oncology (ASCO) website ([www.asco.org](http://www.asco.org)).

(b) Chronologic age may not correlate with physiologic impairment and decline in functional reserve, which vary substantially among individuals. Therefore, treatment for older adults should focus on the extent of comorbidity and functional status (NCCN, 2021d).

(c) Cognitive impairment or decline may affect comprehension and adherence to therapies (NCCN, 2021d; Whitman et al., 2021).

(d) Polypharmacy is more common in older adult patients and increases the risk for drug interactions (Whitman et al., 2021).

- (3) Pediatric oncology: Safe administration of chemotherapy in pediatric patients requires a specialized knowledge set. The Association of Pediatric Hematology/Oncology Nurses provides resources for pediatric oncology nurses ([www.aphon.org](http://www.aphon.org)).

k) Physical examination

- (1) A complete physical examination should be documented in the patient's medical record.
- (2) It should be reviewed prior to initiating a new therapy.

- (3) Any abnormalities should be noted and used as a comparison for future assessments.

l) Pregnancy

- (1) Pregnancy testing is recommended prior to treatment. Few formal guidelines are available regarding pregnancy screening protocols, and a lack of consensus exists regarding the frequency of testing (Association for Clinical Oncology, 2020; Berger et al., 2019; Neuss et al., 2016).

(a) Institutions should develop pregnancy screening protocols that have inclusion criteria (e.g., age 12–55 years, menstrual status), exclusion criteria (e.g., hysterectomy, laboratory tests confirming menopause), time of testing (e.g., within seven days of treatment) and frequency of testing (e.g., every 30 days). Additional factors to consider are intrauterine devices and tubal ligations. If applicable, declaration forms should be considered to document that patients understand the potential harm to a developing fetus and agree to proceed without testing.

(b) Use of prechemotherapy checklists and orders for point-of-care pregnancy tests has been found to improve pregnancy screening rates (Rogers et al., 2017).

- (2) Consensus guidelines for cancer chemotherapy during pregnancy have been developed (Amant et al., 2019).

(a) Patients should be managed by an interprofessional team, including the oncologist, maternal-fetal medicine team, and psychological, social, and spiritual support team members, as indicated or requested.

(b) Risk to the fetus is dependent on the gestational age and the planned agents to be administered.

(c) Chemotherapy is contraindicated during the first trimester because of the increased risk of spontaneous abortions, fetal death, and major congenital malformation (Amant et al., 2019).

(d) Fetal benefit of treatment delay until the second trimester should be balanced against maternal risk (Amant et al., 2019). After 14 weeks of gesta-



tion, administration of several chemotherapy drugs is feasible, including taxanes, platinum agents, anthracyclines, etoposide, and bleomycin (Amant et al., 2019).

- (e) Chemotherapy is not recommended beyond a gestational age of 35 weeks because a three-week window between the last cycle of chemotherapy and delivery is important to allow maternal and fetal bone marrow recovery (Amant et al., 2019).

*m) Gender identity*

- (1) Gender identity should be assessed, and the potential impact on drug dosing and other issues surrounding chemotherapy and immunotherapy should be considered.
  - (a) Gender-affirming hormone therapy can impact renal clearance and ideal body weight (Webb et al., 2020).
  - (b) Webb et al. (2020) recommended that medications be dosed on creatinine clearance and ideal body weight calculations consistent with gender identity after patients have been on hormone therapy for six months or longer.
- (2) Electronic health record systems may calculate creatinine clearance for patients who identify as transgender on admission (Webb et al., 2020). The formula to be used should be clarified with the provider and pharmacist.

*n) Initial psychosocial assessment*

- (1) Standardized tools are used to assess psychosocial concerns (Neuss et al., 2016; Pirl et al., 2013).
- (2) The American College of Surgeons Commission on Cancer (2022) requires distress screening as accreditation criteria.
- (3) Distress has been defined as “a multifactorial unpleasant experience of a psychological (i.e., cognitive, behavioral, emotional), social, spiritual, and/or physical nature that may interfere with one’s ability to cope effectively with cancer, its physical symptoms, and its treatment” (NCCN, 2022c, p. DIS-1).
- (4) The NCCN Distress Thermometer is a tool used to screen for distress (NCCN, 2022c; see Appendix F).
  - (a) Patients are asked to rate distress on a 0–10 scale, with 0 representing no

distress and 10 representing extreme distress.

- (b) If clinical evidence of moderate or severe stress exists or if the score exceeds 4, a clinician trained in distress screening should evaluate the cause of distress and ensure that a referral to a clinician qualified to address distress is completed (NCCN, 2022c).
- (5) Regardless of the tool used for distress screening, the following should be assessed:
  - (a) Family structure and dynamics, living conditions, and caregivers
  - (b) Transportation, financial, or insurance issues: Patients receiving sedating premedications or opioids will need transportation to and from treatment.
  - (c) Religious beliefs or spiritual concerns that may affect dietary and other requirements or restrictions
- o) Comprehension of the disease and planned treatment (see Chapter 3)*
  - (1) Teach-back strategies can assess comprehension (Agency for Healthcare Research and Quality, 2020).
  - (2) Teach-back is a method to assess understanding by asking patients to state, in their own words, the information they have been taught.
  - (3) Using teach-back strategies for assessing comprehension in patients receiving oral chemotherapy has improved patient adherence to treatment (Bellomo, 2016).
- p) Informed consent:* Verify that the informed consent document has been completed and is accurate and current (see Chapter 2). Confirm that issues related to biosimilar substitution have been addressed in the consent process.
- 3. At each clinical encounter related to treatment (e.g., office visit prior to treatment, hospitalization for inpatient treatment, infusion visit), assess the following (Neuss et al., 2016):
  - a) Performance status:* Performance status measures the patient’s functional capacity, including the ability to perform activities of daily living (Neuss et al., 2016).
    - (1) Performance status is used to predict patient tolerance and response to treatment (Jang et al., 2014).
    - (2) Different tools used to assess performance status include the Eastern Cooperative Oncology Group Performance Sta-

- tus Scale and the Karnofsky Performance Status Scale (see Chapter 4).
- (3) The literature reports conflicting data regarding the reliability of performance status measurements, with variable levels of inter-rater reliability (Chow et al., 2020).
- b) Vital signs
- (1) Monitor vital signs before each treatment.
  - (2) Assess for abnormal vital signs (e.g., increased temperature, which could indicate an infection) and adverse reactions to previous doses (e.g., bevacizumab can cause hypertension).
- c) Height and weight: Monitor the patient's height and weight at least weekly when present in the healthcare setting (Neuss et al., 2016). The following are recommended by the Institute for Safe Medication Practices [ISMP] (2022).
- (1) Accurately measured height and weight are imperative for correct dosing of weight-based drugs.
  - (2) One of the most commonly reported medication errors related to dose is inaccurate height and weight.
  - (3) Avoid using stated or estimated height or weight from a previous encounter.
  - (4) Measure and document weight in metric units.
  - (5) Place a conversion chart near all scales so that patients and caregivers can be told the weight in pounds when requested.
  - (6) If purchasing scales, buy scales that measure in kilograms or can be locked out to measure in metric units only.
  - (7) Computer screens and IV infusion pumps should prompt patient weight in metric units only.
- d) Physical examination: Perform an assessment prior to each treatment.
- (1) Assessment should include but not be limited to orientation, level of consciousness, signs of infection, nutritional status, indicators of pain, toxicities from previous doses, and any change that may preclude patients from treatment (e.g., new onset of tachycardia, arrhythmia, shortness of breath, syncope).
  - (2) Perform a focused assessment based on the potential adverse reactions of the agents to be administered.
  - (3) For patients with vascular access devices, assess patency, including a blood return, and for signs of complications.
- (4) Notify the provider of any signs of infection.
    - (a) The treatment plan and assessment findings are considered when deciding to hold or continue therapy when a patient has a fever.
    - (b) For example, the provider may elect to proceed with treatment in a patient with an uncomplicated urinary tract infection receiving a non-myelosuppressive agent.
- e) Symptom assessment: Assess symptoms using an evidence-based patient-reporting tool.
- (1) Patient-reported outcomes are recommended as the preferred method to screen for symptoms because of underdetection of symptoms by healthcare providers. These outcomes are defined as any report of a health condition that comes directly from the patient without interpretation by the clinician (Pirschel, 2017).
  - (2) The Oncology Nursing Society (ONS) has established criteria for patient-reported outcome assessment tools and lists instruments that meet these criteria on its website ([www.ons.org/explore-resources?display=results&source=1476](http://www.ons.org/explore-resources?display=results&source=1476))
- f) Toxicity grading: Grade toxicities found during the physical examination and symptom assessment (Neuss et al., 2016).
- (1) Grading is used to standardize communication among healthcare providers. Toxicity grades can be included as parameters to withhold, delay, or dose-reduce treatment. They are also included as part of clinical trials.
  - (2) The National Cancer Institute Cancer Therapy Evaluation Program's Common Terminology Criteria for Adverse Events tool (v.5.0) is available at [https://ctep.cancer.gov/protocoldevelopment/electronic\\_applications/docs/CTCAE\\_v5\\_Quick\\_Reference\\_5x7.pdf](https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf). Different versions of the tool exist, making it essential to verify the current version of the literature.
- g) Laboratory values: Review laboratory values prior to each treatment.
- (1) Laboratory tests are specific for the agent, regimen, and individual patient. They may be ordered to calculate doses (e.g., serum creatinine for carboplatin), assess for toxicities from prior treatments (e.g., myelosuppression), and ensure that the agent will be adequately metabolized and excreted.

- (2) Determine if the values meet predetermined parameters, which can be included on the treatment orders or listed in a policy or procedure. Parameters to hold the agent or reduce the dose depend on therapy, regimen, and patient goals.
- (3) Examples of laboratory tests
  - (a) Complete blood count and differential: Evaluate results to determine if the dose should be delayed or reduced.
    - i. Parameters for holding therapy should be defined by the practice or prescriber. This can be done based on the individual patient via a specific provider order or a regimen guideline approved for a specific diagnosis. For example, in patients with solid tumors, a parameter to hold treatment or clarify with the prescriber might be an absolute neutrophil count of less than  $1,500/\text{mm}^3$  and a platelet count less than  $100,000/\text{mm}^3$ .
    - ii. Red blood cell count, hemoglobin, and hematocrit should be evaluated to determine if the patient is anemic; however, anemia is usually not an indication to hold chemotherapy.
  - (b) Serum creatinine and creatinine clearance
    - i. Serum creatinine and creatinine clearance are used to calculate doses of carboplatin.
    - ii. Many agents are excreted renally, such as carboplatin, cisplatin, cyclophosphamide, and pemetrexed (Krens et al., 2019). These agents require dose reduction for impaired renal function because renal impairment can cause delayed excretion and increased toxicities.
    - iii. Renal function is also monitored to assess for nephrotoxicity from agents such as cisplatin, high-dose methotrexate, and mitomycin C (Krens et al., 2019).
    - iv. Immune checkpoint inhibitors can cause renal damage, including tubule-interstitial nephritis and immune complex glomerulonephritis (NCCN, 2021c).
  - (c) Total bilirubin and liver function tests
    - i. Many agents are metabolized and cleared from the body by the liver; therefore, dose reductions may be needed for patients with impaired liver function (Krens et al., 2019).
    - ii. Some chemotherapy and immunotherapy agents can also cause hepatotoxicity (Krens et al., 2019). Immune checkpoint inhibitors can cause autoimmune hepatitis with elevated alanine transaminase and aspartate transaminase (NCCN, 2021c).
  - (d) Electrolytes (e.g., calcium, magnesium, potassium): Nephrotoxic agents such as cisplatin can cause electrolyte wasting (Workeneh et al., 2021). The most common laboratory abnormality reported with cisplatin is hypomagnesemia, with incidences reported as high as 91.8% (Workeneh et al., 2021).
  - (e) Hepatitis B testing: Patients with cancer receiving chemotherapy or immunotherapy who are hepatitis B positive are at increased risk for hepatitis B reactivation with the initiation of chemotherapy and immunotherapy (Hwang et al., 2020).
    - i. The risk of hepatitis B reactivation among patients with solid tumors is less than for patients with hematologic malignancies, particularly those receiving anti-CD20 therapies or who have received a stem cell transplant (Hwang et al., 2020).
    - ii. Guidelines for screening hepatitis B and testing
      - The Centers for Disease Control and Prevention recommends prechemotherapy hepatitis B screening for all patients receiving cytotoxic or immunosuppressive therapy (Weinbaum et al., 2008).
      - ASCO (Hwang et al., 2020) recommends that all patients

with cancer anticipating systemic anticancer therapy should be tested for hepatitis B with the following tests: hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc) total immunoglobulin (Ig) or IgG, and antibody to hepatitis B surface antigen (anti-HBs) prior to or at the beginning of systemic anticancer therapy.

- The American Gastroenterological Association recommends screening (HBsAg and anti-HBc, followed by a sensitive hepatitis B virus DNA test if positive) in patients at moderate or high risk who are receiving immunosuppressive drug therapy. They suggest against routinely screening patients who will receive immunosuppressive agents at low risk (Reddy et al., 2015).
- All patients receiving anti-CD20 monoclonal antibodies should be screened for hepatitis B (Hwang et al., 2020; Reddy et al., 2015). Anti-CD20 monoclonal antibodies include obinutuzumab, ofatumumab, and rituximab.

(f) Thyroid function tests: Immune checkpoint inhibitors, such as nivolumab, ipilimumab, and pembrolizumab, can cause endocrinopathies, such as hypothyroidism. NCCN (2021c) guidelines recommend a thyroid-stimulating hormone and free thyroxine ( $T_4$ ) every four to six weeks during immune checkpoint inhibitor therapy and then every 12 weeks as indicated.

(g) Serum cortisol tests (morning preferred) are recommended prior to each treatment or every four to six weeks in patients receiving specific immune checkpoint inhibitors, including ipilimumab (NCCN, 2021c).

h) Diagnostic tests: Review diagnostic tests pertinent to the specific agent.

## (1) Cardiac testing

### (a) Echocardiogram

- i. Echocardiographic imaging is crucial for managing patients treated with cardiotoxic anti-neoplastic agents.
- ii. Left ventricular ejection fraction is the most commonly used parameter for identifying left ventricular dysfunction before, during, and after cancer therapy.
- iii. A complete echocardiogram and strain imaging echocardiogram measure left ventricular dysfunction. A strain imaging echocardiogram also measures global longitudinal strain, which measures cardiac contractile function, an early marker of cardiotoxicity (J.E. Liu et al., 2020).
- iv. Patients receiving anthracycline antitumor antibiotics (e.g., doxorubicin) should have a baseline echocardiogram to evaluate left ventricular ejection fraction (Lexicomp, 2021b). Recommendations to repeat echocardiograms are dependent on the agent and cumulative dose.
- v. In the adjuvant setting, product labeling for trastuzumab recommends an echocardiogram at baseline, every three months during treatment, and every six months for two years following treatment (Genentech, 2021a). If trastuzumab is held because of decreased left ventricular ejection fraction, patients should have repeat monitoring four weeks after discontinuation (Genentech, 2021a).

(b) Electrocardiogram: A baseline electrocardiogram should be performed before starting agents with the potential to prolong QT intervals (Duan et al., 2018). The frequency of follow-up electrocardiograms varies with the agent. The corrected QT, known as QTc, considers the patient's heart rate.

- (2) Pulmonary testing
    - (a) Pulmonary function tests may be ordered prior to initiating bleomycin and at intervals throughout treatment; however, effectiveness in detecting changes from bleomycin is controversial (Roncolato et al., 2016). Spirometry and diffusing capacity for carbon monoxide are typically ordered.
    - (b) Some recommendations advocate chest x-rays or computed tomography scans at intervals throughout bleomycin treatment (Khan et al., 2016).
    - (c) Chest computed tomography scans are recommended to detect interstitial pneumonitis, which can be caused by numerous agents, including immune checkpoint inhibitors (NCCN, 2021c).
    - (d) Pulmonary function tests may be indicated prior to and during other cancer treatment regimens and in patients with preexisting pulmonary issues.
  - i) Psychosocial concerns: Assess psychosocial concerns at each visit.
    - (1) NCCN recommends completion of distress screening at medical visits, including chemotherapy and immunotherapy treatments (NCCN, 2022c; see Appendix F).
    - (2) ASCO/ONS Chemotherapy Administration Safety Standards recommend psychosocial assessment with each cycle and more frequently as indicated (Neuss et al., 2016).
    - (3) At a minimum, distress screening should occur at the initial visit, at appropriate intervals, and as clinically indicated (e.g., changes in disease status, such as recurrence and progression) (NCCN, 2022c).
  - j) Allergies and previous treatment-related reactions should be reviewed and updated at each visit.
  - k) The medication list should be reviewed and updated at each visit.
- C. Chemotherapy, targeted therapy, and immunotherapy dosing
1. Dose calculation includes the calculation methodology, variables used to calculate the dose, frequency at which the variables are reevaluated, and changes in the values that prompt confirmation of dosing (Neuss et al., 2016).
  2. Different dosing methods may be used to calculate doses, depending on the agent and regimen ordered.
    - a) Fixed dosing (flat dosing) is not based on the patient's height or weight.
      - (1) Many oral agents are prescribed in fixed doses. Be aware of agents that may be ordered as fixed doses or based on body surface area (BSA) (e.g., bleomycin fixed dose of 30 units or BSA dose of 10 units/m<sup>2</sup>). Confirm with a reference if the agents in the regimen are a fixed dose or based on BSA or weight alone.
      - (2) According to an ASCO consensus panel, except for bleomycin, no data support the use of fixed dosing for cytotoxic agents (i.e., traditional chemotherapy agents). The practice of limiting vincristine doses to 2 mg in clinical trial protocols is not supported by existing data. Refer to the consensus statement for additional details and clarifications (Griggs et al., 2022).
    - b) Weight-based dosing is expressed as drug dose per unit of body weight (e.g., mg/kg).
    - c) Most chemotherapy agents are dosed using the patient's BSA (m<sup>2</sup>).
      - (1) BSA is a function of height and weight. It can be calculated using a variety of formulas, including the Du Bois and Du Bois formula and the Mosteller formula (see Figure 11-1). ASCO recommends that BSA be calculated using standard formulas. No evidence supports one formula for calculating BSA over another (Griggs et al., 2021).
      - (2) The calculated BSA is then multiplied by the dose in mg/m<sup>2</sup>, mcg/m<sup>2</sup>, or g/m<sup>2</sup> to determine the total dose of the agent to be administered. To prevent errors, institutions should standardize milligrams (mg) or grams (g) in orders and pump error prevention programming (i.e., methotrexate should not appear in milligrams in the order set but in grams in the pump error prevention program).
      - (3) The underlying assumption for dosing based on BSA is that BSA is a more reliable indicator than using weight alone for predicting pharmacokinetics. However, BSA dosing does not consider factors such as gender and age.
      - (4) In most situations, no significant difference exists between doses calculated using different BSA formulas (Faisal et al.,

**FIGURE 11-1.** Calculating Chemotherapy Dose Using Body Surface Area**Formulas to calculate estimated body surface area (BSA)**

- Du Bois and Du Bois:  $BSA (m^2) = \text{Weight (kg)}^{0.425} \times \text{Height (cm)}^{0.725} \times 0.007184$
- Mosteller (metric):  $BSA (m^2) = \sqrt{[(\text{Height (cm)} \times \text{Weight (kg)}) / 3,600]}$

**To calculate the total dose of chemotherapy or immunotherapy**

Calculated BSA ( $m^2$ )  $\times$  dose in  $mcg/m^2$ ,  $mg/m^2$ , or  $g/m^2$  = total dose of chemotherapy

**Example**

The patient is 157.48 cm tall and weighs 60 kg. She is scheduled to receive paclitaxel 80  $mg/m^2$  IV.

- Using the Mosteller formula, calculate the BSA.
  - Multiply height and weight using metric units.  
 $157.48 \text{ cm} \times 60 \text{ kg} = 9,448.8$
  - Divide the total by 3,600.  
 $9,448.8 / 3,600 = 2.6246$
  - Using a calculator, determine the square root.  
Square root =  $1.62 \text{ m}^2$
- Calculate the total dose by multiplying the BSA by the dose ordered in  $mg/m^2$ .  
 $1.62 \text{ m}^2 \times 80 \text{ mg/m}^2 = 129.6 \text{ mg}$

Note. Based on information from Du Bois & Du Bois, 1916; Mosteller, 1987.

2016). However, different formulas may produce different results for patients with extremes in height or weight (Faisal et al., 2016; Fancher et al., 2016).

- (5) The Mosteller formula can be easily performed using any calculator with a square root function.
  - (6) If the electronic health record calculates BSA, verify the formula and use it when recalculating doses during order verification.
- d) Carboplatin is dosed using area under the curve (AUC)-based dosing, which refers to the amount of drug exposure or total drug concentration in plasma over time.
- (1) AUC dosing considers age, gender, weight, and renal function.
  - (2) Carboplatin drug clearance is strongly correlated with renal function.
  - (3) Carboplatin doses are determined by first calculating the creatinine clearance and then calculating the total dose of carboplatin by using the Calvert formula (see Figure 11-2). AUC is prescribed in the treatment plan and usually ranges from 2 (low dose) to 6 (higher dose).
    - (a) To calculate creatinine clearance, estimated creatinine clearance is often used rather than an actual glomerular filtration rate (24-hour urine for creatinine clearance).
    - (b) Many formulas are used to calculate creatinine clearance, with the

Cockcroft-Gault being the most common in the United States.

- (c) To calculate creatinine clearance using the Cockcroft-Gault formula, the patient's age, gender, weight in kilograms, and recent serum creatinine are obtained (see Figure 11-3). The formula may not be accurate in patients with rapidly changing serum creatinine levels (Gaguski & Karcheski, 2011).
- (d) The National Cancer Institute (2010) recommends capping estimated serum creatinine clearance at 125 mL/min to prevent overdosing and dose capping carboplatin based on AUC (see Figure 11-4).
- (e) Additional considerations in carboplatin calculations (NCCN, 2020)
  - i. Consider using an adjusted body weight for patients characterized as overweight or obese (body mass index

**FIGURE 11-2.** Calculating Carboplatin Dose Using the Calvert Formula

Dose of carboplatin (mg) = (target AUC)  $\times$  (GFR + 25)

Total dose calculated is in mg, not  $mg/m^2$ .

AUC—area under the plasma concentration versus-time curve; GFR—glomerular filtration rate

Note. Based on information from Calvert et al., 1989.



**FIGURE 11-3.** Calculating Glomerular Filtration Rate Using the Cockcroft-Gault Formula**Males**

$$\text{estCrCl (ml/min)} = \frac{(140 - \text{age}) \times (\text{weight in kg})}{72 \times \text{serum creatinine (mg/dl)}}$$

**Females**

$$\text{estCrCl (ml/min)} = \frac{(140 - \text{age}) \times (\text{weight in kg}) \times (0.85)}{72 \times \text{serum creatinine (mg/dl)}}$$

estCrCl—estimated creatinine clearance

Note. Based on information from Cockcroft &amp; Gault, 1976.

greater than or equal to 25 kg/m<sup>2</sup>): adjusted body weight (kg) = ideal body weight + 0.4 × (total body weight – ideal body weight).

- ii. For patients with abnormally low serum creatinine, including older adults or cachectic patients, consider using a minimum serum creatinine of 0.7 mg/dl to avoid overestimated creatinine clearance.

- iii. Consider using ethylenediaminetetraacetic acid or 24-hour urine testing to measure creatinine clearance (not Cockcroft-Gault or another formula) when dosing AUC greater than 6 or when using an uncapped creatinine clearance.

- (f) If variance exists between the prescribed dose and the recalculated dose, clarify with the prescriber whether the actual, adjusted, or ideal

weight was used when calculating creatinine clearance and whether an adjusted serum creatinine was used.

## 3. Dosing and obesity

- a) Controversy exists regarding dosing for patients characterized as obese. Concerns voiced include fears of toxicity versus compromising disease-free survival in the curative setting (Furlanetto et al., 2016). ASCO has developed formalized guidelines for this population (Griggs et al., 2021).

- (1) Full, weight-based cytotoxic chemotherapy doses should be used to treat obese adults with cancer.
- (2) An adult with a body mass index of 30 kg/m<sup>2</sup> or greater is considered obese.
- (3) Fixed dosing of chemotherapy should be limited to selected agents (e.g., bleomycin).
- (4) U.S. Food and Drug Administration prescribing information for immune checkpoint inhibitors should be used in all patients regardless of obesity status.
- (5) Clinicians should follow the same dose reduction guidelines for patients characterized as obese and nonobese.

- b) Actual body weight is recommended for BSA and weight-based dosing; however, NCCN (2020) recommends using adjusted body weight for overweight or obese patients (body mass index greater than or equal to 25 kg/m<sup>2</sup>) when calculating creatinine clearance for carboplatin dosing.

## 4. Dosing and underweight patients

- a) No formal guidelines exist addressing the dosing of underweight patients, those with low body mass index, or those with low skeletal mass (Griggs et al., 2021).
- b) Preterm termination of chemotherapy is associated with lower body mass index (Grabowski et al., 2018).

## 5. Dose rounding

- a) Institutional dose-rounding policies and practices should be followed when calculating and verifying doses.
- b) These policies often allow dose rounding at 5%–10% of the prescribed therapy. Policies may also differentiate between chemotherapy and immunotherapy doses, the intent of therapy (cure vs. palliation), and whether doses can be rounded up, down, or both. Some institutions may not allow dose rounding for pediatric patients. Clinical trials may specify the accepted percentage for dose rounding.
- c) Hematology/Oncology Pharmacy Association (2017) dose-rounding recommendations

**FIGURE 11-4.** Calculating Carboplatin Dose Capping Using Estimated Creatinine Clearance

$$\text{Dose of carboplatin (mg)} = (\text{target AUC}) \times (\text{estCrCl} + 25)$$

estCrCl capped at 125 ml/min

Maximum doses for sample target AUCs

- Target AUC 6:  
Maximum carboplatin dose = 6 × (125 + 25) = 900 mg
- Target AUC 5:  
Maximum carboplatin dose = 5 × (125 + 25) = 750 mg
- Target AUC 4:  
Maximum carboplatin dose = 4 × (125 + 25) = 600 mg

AUC—area under the plasma concentration versus-time curve; estCrCl—estimated creatinine clearance

Note. Based on information from Calvert et al., 1989.

- (1) For monoclonal antibodies, other immunotherapies, and traditional cytotoxic chemotherapy, round the dose to the nearest vial size within 10% of the prescribed dose.
- (2) For monoclonal antibodies with conjugated (attached) cytotoxic agents, apply dose rounding to the cytotoxic component of the agent. It can be rounded to the nearest vial size within 10% of the prescribed dose.
- (3) For oral chemotherapy, use one dose strength and round the final dose, when possible, to simplify dosing for patients.
- (4) Dose rounding can be used for curative and palliative therapy if the rounding does not influence clinical safety or effectiveness.

#### D. Verification

1. The healthcare setting should have established processes for verification and clearly defined steps to take when discrepancies arise (Neuss et al., 2016). Verification refers to determining the accuracy of the prescribed therapy, prepared medication, patient identification, and pump settings (if applicable).
2. Verification should occur prior to administration for all chemotherapy, targeted therapy, and immunotherapy routes, including the oral route.
  - a) Independent dual verification (i.e., independent double-check) is a process in which a second person conducts an independent verification of the accuracy of the prescribed therapy without telling their findings to the other verifier until both have completed the process (ISMP, 2019).
  - b) Numerous studies have demonstrated that independent double-checks of medication can detect up to 95% of errors (Alsulami et al., 2012). Checklists may help promote a consistent process (see Appendix D).
3. Verification step 1: Verify the accuracy of the treatment plan (chemotherapy orders).
  - a) Verify a minimum of two patient identifiers per institutional policy, such as name, date of birth, and medical record number. Do not use room or chair numbers as patient identifiers (Neuss et al., 2016).
  - b) Compare the treatment plan with a reference for doses, routes, and schedule. For example, orders for doxorubicin 60 mg/m<sup>2</sup> IV and cyclophosphamide 600 mg/m<sup>2</sup> IV every two weeks for four cycles are compared with a reference. This confirms the doses, routes, and schedule. Never verify accuracy by comparing previous patient doses, as they may have been changed because of toxicities or weight change.
- c) Confirm the accuracy of the treatment plan cycle and day number.
  - (1) Compare the date on the orders, date of planned therapy, and previously administered doses. For example, the patient is scheduled for cycle 12 of weekly paclitaxel, but the nurse notes from the medical record that the patient has received 10 doses.
  - (2) Confirm that the appropriate interval has occurred between treatments (e.g., seven days between paclitaxel doses).
- d) Compare the height and weight on the treatment plan with the current measured height and weight.
- e) BSA-dosed medications
  - (1) Recalculate the BSA based on the current measured height and weight. Compare the recalculated BSA with the one on the treatment plan.
  - (2) Recalculate the total dose and compare it with the prescribed dose.
- f) For carboplatin, recalculate the patient's creatinine clearance. Recalculate the total dose using the Calvert formula. Compare the recalculated dose with the prescribed dose.
- g) For weight-based medications, recalculate the total dose.
- h) For fixed-dose medications, compare the prescribed dose with a reference.
- i) Institutional policy and procedure should define changes in values that prompt a call to the provider to determine if recalculation or dose adjustment is needed (Association for Clinical Oncology, 2020). For example, an institutional policy may state that a 10% change in weight would prompt a call to the provider to determine if the dose should be changed to reflect the weight change. Some electronic health records will alert the provider to identified changes in weight or BSA.
- j) Verify the route of administration, sequence of administration, and the duration of infusion, if applicable.
  - (1) The sequence in which chemotherapy and immunotherapy are given may affect the pharmacokinetics and pharmacodynamics of the agents and thus, efficacy and toxicity.
  - (2) Lehman et al. (2019) developed a sequencing table to guide staff when evidence for sequencing exists.
  - (3) If sequencing data are not available, institutions should follow the original sequence in the clinical trial.



- (4) For administration through peripheral IVs, vesicant status should also be considered in sequencing, as venous integrity decreases over time.
  - k) Verify the compatibility of any IV solutions and medications used during administration.
  - l) Confirm that supportive care treatments are ordered and are appropriate to the regimen (e.g., premedications, hydration, growth factors, rescue agents, medications to manage infusion reactions).
  - m) Clarify any discrepancies with the prescriber before initiating treatment. Common discrepancies include inaccurate height and weight and different formulas for calculating BSA or creatinine clearance.
4. Verification step 2: Check the prepared medication.
  - a) Compare the medication and label with the treatment plan (orders) and verify the following:
    - (1) Patient name, date of birth, and any other identifier established in institutional policy
    - (2) Medication name and total dose
    - (3) Diluent type and total volume (as appropriate)
    - (4) Expiration date and time
  - b) Assess the appearance and physical integrity of the medication and medication container (e.g., clarity, leaking).
  - c) Check any special labeling (e.g., HDs, for IV use only, protect from light).
  - d) Verify that the correct type of tubing and filter is attached, if applicable.
  - e) Confirm the presence of a closed-system drug-transfer device (CSTD) on parenteral preparations.
5. Verification step 3: Verify the patient, medication, and pump programming at the bedside (or chair-side).
  - a) Prior to placing an identification band or label on the patient, always confirm the patient's stated name and birthdate with the identification band or label.
    - (1) Do not assume that the patient's identification band is correct without patient verification.
    - (2) For non-English-speaking patients, an interpreter should be used to confirm patient identity prior to wrist band application.
  - b) Immediately prior to administration, the following should be verified by two practitioners approved by the healthcare setting:
    - (1) Compare the patient's stated name, birthdate, and any other institutional identifiers on the patient's identification band or sticker and the medication label.
  - (2) Compare the medication name, dose, route, and schedule on the label with the treatment plan.
  - (3) Where scanning is available, scan the patient's wristband with the medication label. Scanning does not eliminate the action of verifying the patient's stated name and birthdate.
    - (a) No studies exist investigating the accuracy of scanning replacing two-practitioner bedside verification.
    - (b) Numerous studies and recommendations support barcoding and scanning for medication administration (Seibert et al., 2014). Advantages reported included increased accuracy, elimination of the need to find another practitioner who may be busy, improvement in verification time, and elimination of bias.
    - (c) Limitations of barcode scanning
      - i. Failure to detect the incorrect route of administration
      - ii. Poor practices involving using scanning identification barcodes not attached to patients
      - iii. Possibility of incorrect barcodes
      - iv. Overreliance on technology (Michalek & Carson, 2020)
      - v. Barcode scanning not detecting an error if the wrong patient identification band or label is applied to patients
  - c) Verify any infusion pump programming with the treatment plan and reference (Neuss et al., 2016).
6. Include the patient as part of the verification process.
  - a) Involve patients and families in the medication verification process by providing them with the medication names, schedule, potential adverse reactions, and indications of when to notify the healthcare provider.
  - b) Encourage patients to alert their nurse to clarify any possible discrepancies (e.g., "I thought today was my last chemotherapy, not next week," "Is it OK for me to get my 5-fluorouracil if I have diarrhea six to eight times a day?") (Agency for Healthcare Research and Quality, 2021; Hartkopf Smith, 2009a; Schwappach et al., 2018).
  - c) Individuals with limited English fluency are at high risk for medical errors and serious adverse

events (Perez et al., 2016; Wasserman et al., 2014). The use of medical interpreters, including video services, has decreased these errors (Nápoles et al., 2015).

#### E. Routes of chemotherapy, immunotherapy, and targeted therapy administration

##### 1. Oral route

*a)* Oral cancer treatments have experienced a rapid increase over the past 10 years with new cytotoxic agents, small molecule inhibitors, and other targeted therapies. The oral route presents unique challenges for oncology nurses and patients as treatment shifts from clinician-administered therapy in a healthcare setting to self-administration.

*b)* Pretreatment assessment (in addition to the general pretreatment assessment) (Multinational Association of Supportive Care in Cancer, 2016; Neuss et al., 2016; ONS, 2016)

- (1) Financial/insurance coverage for the medication and available pharmaceutical company assistance programs
- (2) Method or location the patient will obtain the medication (e.g., specialty pharmacy, drop shipment)
- (3) The patient's ability to swallow and retain pills (e.g., dysphagia, strictures, presence of gastrostomy or jejunostomy tube, mucositis, esophageal strictures, vomiting)
- (4) The patient's ability to read labels, instructions, and calendars
- (5) The patient's ability to open medication bottles or packages
- (6) The patient's ability to comprehend instructions regarding dosing, schedules, and indications to hold medication and notify the healthcare provider
- (7) Possible food–drug interactions, drug–drug interactions, and supplement–drug interactions

*c)* System safeguards to prevent errors and manage emergencies (see Chapters 1, 12, and 13)

- (1) Independent practitioners qualified by the healthcare setting should sign oral chemotherapy, targeted therapy, and immunotherapy orders to treat cancer (Neuss et al., 2016).
- (2) Information to include in prescriptions or orders for oral chemotherapy, targeted therapies, and immunotherapy (Neuss et al., 2016; ONS, 2016)
  - (a)* Patient name, date of birth, and any institution-specific identifiers

*(b)* Full generic name of the medication

*(c)* Drug dose and calculation methodology (e.g., mg/m<sup>2</sup>)

*(d)* Schedule of administration

*(e)* Drug quantity to be dispensed and the number of refills, with zero as the acceptable default value; a time limitation to refills helps ensure appropriate evaluation at predetermined intervals.

*(f)* Any special instructions

(3) Institutional policies should address the process for continuing oral chemotherapy, targeted therapy, and immunotherapy when patients are admitted to the hospital.

*(a)* In many settings, patients may be admitted by a hospitalist or other non-oncologist. The potential for error exists if the therapy is continued as part of a home medication list; however, it may be contraindicated for the patient's current condition (Booth et al., 2011; Schleisman & Mahon, 2015).

*(b)* Prior to giving an oral chemotherapy, targeted therapy, or immunotherapy agent in the inpatient setting as a continuation of home therapy, verify that the agent was ordered by a licensed independent practitioner qualified by the healthcare setting and that the therapy is appropriate to continue and at the same dose.

*d)* Dosing: When possible, one dose strength of pill should be used and rounded to the final dose (Hematology/Oncology Pharmacy Association, 2017).

*e)* Verification (see section D)

*f)* Administration

(1) Do not crush hazardous oral antineoplastics outside of a containment primary engineering control. If the patient cannot take oral medication, discuss an alternative route with the oncologist or use strategies for safe administration (Polovich & Olsen, 2018; see Chapter 12).

(2) For intact oral tablets, capsules, or pills designated as hazardous, wear one pair of gloves tested for use with HDs. A mask with a face shield and double gloves should be worn if the potential for sprays, aerosols, or splattering of the agent exists, such as with liquid oral HDs (Polovich & Olsen, 2018).

*g)* Other considerations

- (1) The institution or practice should determine a process to assess and track patient adherence to oral cancer therapy (Neuss et al., 2016; ONS, 2016).
  - (2) Strategies to encourage adherence include calendars or daily medication checklists, pill diaries, electronic reminders, and text messages (Burhenn & Smuddle, 2015; ONS, 2016; Rodriguez et al., 2017; Spoelstra & Sansoucie, 2015; see Chapter 4).
  - (3) Set up routine appointments to monitor patient response to therapy, including follow-up laboratory testing.
  - (4) Information to include in patient education (ONS, 2016)
    - (a) Drug name, dose, and schedule, including calendar as appropriate
    - (b) How the drug will be obtained
    - (c) Potential side effects, management, and indications for when to notify the healthcare provider
    - (d) Safe storage and handling
    - (e) Disposal of unused medication (e.g., drug drop-off sites that accept HDs)
    - (f) Food, drug, and supplement interactions
    - (g) Plan for missed doses
    - (h) Schedule of appointments for monitoring
    - (i) Process for refills
2. SC and intramuscular (IM) routes
- a) Few chemotherapy, targeted, and immunotherapy agents are administered via the SC or IM route. Select hormone agents used as antineoplastics are administered via these routes. See Tables 6-1, 7-1, 8-1, and 10-1 for a listing of drugs given via these routes.
  - b) Pretreatment assessment (in addition to the general pretreatment assessment)
    - (1) Assess for adequate SC or muscle sites.
    - (2) Review any coagulation values and other risks for bleeding and bruising.
  - c) System safeguards to prevent errors and manage emergencies (see Chapters 1, 12, and 13): Never administer vesicants by the SC or IM route.
  - d) Dosing: The medication may have to be divided into several syringes, depending on the total volume of the syringe.
    - (1) The maximum volume for IM injections varies according to muscle mass and the muscle used, with the deltoid muscle ranging 0.5–2 ml, the dorsogluteal 4 ml, and the vastus lateralis 5 ml (Hopkins & Arias, 2013).
    - (2) The maximum volume for SC injections varies according to the amount of SC muscle and the injection location, with a volume range of 2–3 ml (Ferruccio et al., 2016).
      - (a) Exceptions include preparations that include hyaluronidase. The addition of hyaluronidase, an enzyme that increases the distribution and absorption of locally injected substances, permits the large volume of SC injection. An example is rituximab and hyaluronidase human, for which the total volume of SC injection is 11.7 ml or 13.4 ml, depending on the dose (Genentech, 2021c).
      - (b) Care must be taken to ensure this formulation is not given via IV.
- e) Verification (see section D)
- f) Administration
- (1) For SC and IM medications designated as hazardous (Polovich & Olsen, 2018)
    - (a) Wear two pairs of gloves, tested for use with HDs, and a gown. Wear a mask with face protection if splashing is possible (see Chapter 12).
    - (b) Use CSTDs attached between the syringe and needle when possible (Polovich & Olsen, 2018).
    - (c) If air bubbles are noted in the syringe, do not express unless in a containment primary engineering control (Polovich & Olsen, 2018; see Chapter 12).
  - (2) Use the smallest gauge needle possible.
  - (3) Review product literature for any specific instructions regarding the site of SC or IM injection. For example, instructions for bortezomib specify injection into the thigh or abdomen (Millennium Pharmaceuticals, 2019). Rituximab hyaluronidase is recommended for abdomen administration only (Genentech, 2021c).
  - (4) Avoid scarred areas.
  - (5) Rotate sites.
  - (6) Clean the site with antiseptic and allow to dry completely prior to injection.
  - (7) For IM injections (Sisson, 2015)
    - (a) Usual sites for delivering an IM injection include the deltoid, vastus lateralis, ventrogluteal, and dorsogluteal muscles.
    - (b) The deltoid, vastus lateralis, and ventrogluteal sites are recommended

because these sites are distant from major blood vessels and nerves. Aspiration is not required for these sites.

- (c) Aspiration is still advised when injecting into the dorsogluteal muscle because of its proximity to the gluteal artery.
  - (8) Consider using the Z-track method to administer agents designated as irritants (Hopkins & Arias, 2013).
  - (9) Inject medication at the prescribed rate.
  - (10) Dispose of any unused supplies in an appropriate waste container.
  - (11) Following administration, assess for pain, swelling, induration, hemorrhage, erythema, pruritus, and rash.
3. IV route
- a) IV administration is one of the most common routes of administration. Medications can be administered depending on the agent and regimen and include IV push, short-term infusion, or continuous IV infusion.
  - b) Pretreatment assessment (in addition to the general pretreatment assessment)
    - (1) Evaluate the patient's venous access. Determine if it is appropriate or adequate for the prescribed therapy.
      - (a) Consider the agents to be administered; their vesicant, irritant, or non-vesicant properties; the prescribed method of administration; and the overall duration of therapy.
      - (b) Refer to ONS's *Access Device Standards of Practice for Oncology Nursing* (Camp-Sorrell & Matey, 2017) and the Infusion Nurses Society's (2021) *Infusion Therapy Standards of Practice*.
      - (c) Long peripheral IVs are sometimes used when the vein is difficult to visualize or palpate, and ultrasound is indicated for placement in deep tissue (Infusion Nurses Society, 2021).
        - i. Do not use long peripheral IVs for continuous infusions of antineoplastic vesicants (Infusion Nurses Society, 2021).
        - ii. Signs and symptoms of extravasation may go undetected due to deep placement.
      - (d) Midline catheters are inserted peripherally into the basilic, brachial, or cephalic vein with the tip in the upper arm at the level of the axilla (Infusion Nurses Society, 2021). Midline catheters are considered peripheral IVs (Infusion Nurses Society, 2021).
        - i. Do not use midlines for continuous infusions of vesicants (Infusion Nurses Society, 2021).
        - ii. Caution is recommended with midlines because of the risk of undetected extravasation, as the vein may be deeper than a traditional short peripheral IV (Camp-Sorrell & Matey, 2017). Further research is needed to establish the safety of using midline catheters for intermittent vesicant therapy (e.g., IV push, intermittent infusion) (Infusion Nurses Society, 2021).
    - (e) Central venous catheters include peripherally inserted central lines, implanted ports, tunneled catheters, and nontunneled catheters.
      - i. The appropriate tip location of a central venous catheter is in the lower third of the superior vena cava or near the cavoatrial junction (Infusion Nurses Society, 2021).
      - ii. Central venous access devices are indicated for continuous infusions of vesicants, vesicants greater than or equal to 30 minutes in duration (excluding medications categorized as irritants with vesicant potential; see Chapter 13), home infusions via ambulatory pumps, and with poor venous access where peripheral access is not possible.
  - (2) Identify risk factors for extravasation if the treatment regimen includes a vesicant (see Chapter 13).
  - (3) Priming IV tubing
    - (a) During the preparation of infusions, IV tubings are most often primed with a compatible fluid rather than the antineoplastic agent itself (see Chapter 12).
    - (b) For medications that require rate increases (e.g., rituximab, carboplatin desensitizations), the tubing should

be primed with the antineoplastic medication and a CSTD attached to the end of the tubing.

- i. Laudati et al. (2018) found that the incidence of infusion reactions with rituximab was significantly less when the line was primed with medication rather than the mainline IV solution.
  - ii. If medication is primed to the end of the IV tubing, strategies to prevent exposure to HDs should be implemented, such as priming the IV line under a biosafety cabinet, labeling the IV tubing as “primed with hazardous medication,” and using a CSTD on the end of the tubing (see Chapter 12).
  - iii. Priming paxlitaxol tubing with drug is also a common practice; however, titration may increase the risk of reaction (refer to Chapter 13).
- c) System safeguards to prevent errors and manage emergencies (see Chapters 1, 12, and 13)
- (1) The institution or practice should define a process to manage the overfill of IV bags (ISMP, 2021).
    - (a) To ensure accurate infusion rates and delivery of the entire medication dose, medication labeling or institutional guidelines should provide the total volume to infuse on the label, including overfill and any additives (ISMP, 2021).
    - (b) Lack of a clear identification of the total volume in the bag can lead to administering the agent too quickly, too slowly, or incompletely.
  - (2) Strategies should be implemented to prevent errors from inadvertent administration of vinca alkaloids into the cerebrospinal fluid (ISMP, 2020b; NCCN, 2016).
    - (a) Administer vinca alkaloids in a minibag (IV piggyback). Never administer using an IV pump when administering through a peripheral IV catheter. Do not administer in a syringe in facilities where intrathecal medications are administered.
    - (b) Label all vinca alkaloid bags “FOR INTRAVENOUS USE ONLY—FATAL IF GIVEN BY OTHER ROUTES.”
    - (c) Never dispense vinca alkaloids to an area where intrathecal medications are administered.
    - (d) Never give vinca alkaloids in the same treatment room as intrathecal medications.
- (3) Ambulatory infusion pumps
- (a) To prevent errors, prescribers should order 5-fluorouracil and other continuous infusion antineoplastics in single daily doses with directions to infuse continuously over a specific number of days (e.g., 750 mg/m<sup>2</sup> IV over 24 hours on days 1–5) (ISMP, 2015a).
  - (b) Numerous errors have been reported regarding home infusions of 5-fluorouracil and are often related to prescribing and pump programming. A common but potentially fatal error is confusing the daily dose with the total dose (ISMP, 2015a, 2015b).
  - (c) Infusion pumps should be used with dose error reduction software when possible (ISMP, 2020).
  - (d) The information the pharmacist or nurse needs to program the pump should be displayed clearly on the medication label (ISMP, 2015a, 2015b).
  - (e) Information to include in patient and caregiver education (ISMP, 2015a)
    - i. Total dose, the length of time the infusion should last, and instruction to routinely check that the pump is not infusing too fast or slow
    - ii. Troubleshooting alarms and infusion pump malfunction
    - iii. Steps to follow if tubing becomes disconnected, a spill occurs, or a port needle becomes dislodged
    - iv. 24-hour contact information for questions and problems
  - (f) The institution or practice should establish a process to address patients who present to emergency departments and inpatient areas with ambulatory infusion pumps with antineoplastic. Often, healthcare providers in these areas are not familiar with certain ambulatory pumps, and patients who use these devices may be ill-informed, leading to severe errors (ISMP, 2015a, 2015b).

- (4) To ensure that premedications and IV hydration have sufficient time to work, administer at the prescribed interval before giving the antineoplastic agent (e.g., diphenhydramine 30 minutes [not 10 minutes] prior to the start of paclitaxel).
- d) Dosing (see section C)
- e) Verification (see section D)
- (1) Verify any infusion pump programming with another provider (Neuss et al., 2016).
  - (2) For continuous infusions in inpatient settings, if another nurse initiated an infusion, the nurse assuming patient care should verify the infusion during shift handoff to prevent the possible propagation of a previous error.
  - (3) When chemotherapy is administered in the home by a healthcare provider, a second identifier, such as a driver's license, should be used to confirm the patient's identity (Neuss et al., 2016).
- f) Administration
- (1) Equipment
    - (a) IV tubing selection
      - i. Standardize the use of IV tubings.
      - ii. Use IV tubings with Luer-lock connections. For HDs, use CSTDs (Polovich & Olsen, 2018; see Chapter 12). Some manufacturers incorporate these devices as part of the IV tubing.
      - iii. Select IV tubing and setups that provide minimal waste of antineoplastic remaining in the IV tubing. This provides the maximum dose to the patient with minimal HD disposal. The primary goal of antineoplastic drug administration should be to ensure patients receive the total dose prescribed.
        - Secondary IV tubings (often called IV piggyback tubing) are short tubings with Y-sites above the pump. The mainline infusion (e.g., 0.9% normal saline, primary IV) automatically shuts off during the infusion and turns back on once completed. Harding et al. (2020) recommended short secondary tubings as the best practice for delivering small-volume intermittent IV infusions. After the HD is administered, the back prime method can be repeated to flush out the drug to ensure full medication delivery (ISMP, 2021; see Chapter 12). Short primary tubing can also be used.
  - (2) Long primary IV tubings used to administer antineoplastics are run on their own pump channel and use a Y-site into a mainline IV below the level of the IV pump, often into the Y-site closest to the patient. The mainline infusion continues during the medication. A large drug volume is often left in the IV tubing despite flushing. Drug loss can be significant, especially if the medication volume is 100 ml or less (Hartkopf Smith & Tanner, 2019; ISMP, 2021). A method must be employed to ensure the drug is not wasted in the tubing. If flushing is done from the HD bag, a CSTD should be used to minimize exposure. The HD bag should never be unspiked to flush.
  - (3) Short primary IV tubings use a Y-site into the mainline IV at a level immediately below the IV pump and run on their own pump channel. Advantages of using short primary tubing include the ability to infuse the mainline IV at the same time as the antineoplastic agent and the minimal amount of waste (less than 1 ml) remaining in the IV tubing after the infusion (Hartkopf Smith & Tanner, 2019). The mainline IV can flush the remaining drug to the patient without any breaks in tubing connections.



- Additional interventions to decrease drug waste in tubing include using microbore tubing and flushing after the medication with the mainline IV solution (ISMP, 2021).
  - Select IV tubing and setups that permit the least amount of system manipulation, thus decreasing the risk of infection for the patient and HD exposure for the healthcare provider.
  - Use IV tubings and setups that allow for emergency response if administering a drug that can cause hypersensitivity reaction or anaphylaxis.
  - The mainline IV should contain a compatible carrier solution that can be turned on immediately after discontinuing the medication causing the reaction.
  - Some medications require DEHP (di[2-ethylhexyl] phthalate)-free tubing (see Tables 6-1, 8-1, and 10-1).
  - DEHP is a plasticizer added to polyvinyl chloride plastic to make it flexible.
  - Some medications cause leaching of DEHP, which may be harmful to patients.
  - Medications may require an in-line filter (see Tables 6-1, 8-1, and 10-1 and drug package inserts).
  - The addition of an antisiphon valve to the end of the IV tubing has been found to minimize bubbles and decrease air alarms in continuous chemotherapy infusions, such as EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) (Meade et al., 2019).
  - The antisiphon valve must be manually primed with a syringe or IV pump because it cannot be primed by gravity. Blood return with this setup must be checked from below (distal to) the valve.
  - For designated HDs, wear two pairs of gloves, tested for use with HDs, and a gown. Wear a mask with face protection if splashing is possible (Polovich & Olsen, 2018; see Chapter 12).
- (b) Use IV pumps with dose error reduction software in inpatient and outpatient settings to administer infusions of chemotherapies, targeted therapies, and immunotherapies, excluding peripheral administration of vesicants (ISMP, 2020). Refer to the ISMP (2020) *Guidelines for Optimizing Safe Implementation and Use of Smart Infusion Pumps*.
- i. Do not rely on pump alarms to detect IV infiltration or extravasation.
  - ii. IV pumps with dose error reduction software are preferred because they include medication dosing guidelines, concentrations, dose limits, and advisories (Infusion Nurses Society, 2021; ISMP, 2020).
  - iii. Infusion interoperability is the ability of an infusion pump to receive and transmit information in near real time with the electronic health record. Medication orders and parameters automatically program the infusion pump. The pump can then send infusion status and history to the electronic health record.
- (2) Peripheral venous access
- (a) Do not use peripheral IV sites to administer vesicants given as continuous infusions. When administering vesicants via a peripheral IV site, limit the infusion time to less than or equal to 30 minutes and remain with the patient during the entire infusion. See Chapter 13 for more information on the administration of drugs with vesicant potential.
- (b) Venipuncture

- i. Avoid using established IV sites that are more than 24 hours old.
  - ii. No clear evidence exists to support the use of a new venipuncture site versus one less than 24 hours old for the administration of vesicants. Regardless, thoroughly assess the site for patency, including blood return before, during, and after administration.
  - iii. Avoid topical anesthetics if peripheral vesicant chemotherapy is planned.
  - iv. Choose veins that are large, smooth, and pliable.
  - v. Sites to avoid
    - Joints and areas near joints
    - Ventral surface of the hand
    - Antecubital fossa
    - Lower extremities
    - Areas distal to a recent venipuncture, including laboratory draws
    - Areas with decreased sensation (e.g., peripheral neuropathy)
    - Areas of impaired circulation or lymph node drainage (e.g., axillary lymph node dissection)
  - vi. No definitive guidelines exist regarding venipuncture in the involved arm of patients who have had a sentinel lymph node biopsy.
  - vii. Ultrasound-guided peripheral catheter insertion in deep veins in the upper arms may be associated with an increased incidence of undetected infiltration and extravasation. Staff skilled in ultrasound-guided IV insertion must ensure sufficient catheter length is threaded into the vein to prevent catheter dislodgment during patient movement. Nurses should assess the vein frequently for signs and symptoms of infiltration (Infusion Nurses Society, 2021).
  - viii. Avoid using metal needles, as they may increase the risk of infiltration or extravasation (Camp-Sorrell & Matey, 2017).
  - ix. Perform venipuncture according to institutional policy and procedure. If unsuccessful, restart IV using a different site on the opposite arm or proximal to the previous puncture site.
  - x. Apply a transparent dressing to the insertion site and secure the catheter. Ensure visualization of peripheral IV entrance site.
  - xi. Ensure securement of the peripheral IV to help prevent dislodgment. In a study examining 673 vesicant extravasations and irritant infiltrations, one of the most common etiologies was patient movement and subsequent dislodgment (Jackson-Rose et al., 2017).
  - xii. Educate patients to report unusual tugging on tubing or IV, discomfort, swelling, or pain during administration.
  - xiii. Before starting chemotherapy administration, flush the IV with a 5–10 ml normal saline syringe and confirm and document a positive blood return. Confirm and document the absence of signs and symptoms of infiltration. Do not administer vesicants in the absence of a blood return or if other signs or symptoms of infiltration are present.
  - xiv. Observe for swelling, pain, burning, tightness, cool skin, skin color change, and changes in flow rate. If infiltration occurs, immediately stop the infusion.
- (3) Central venous access devices include percutaneous subclavian or jugular catheters, tunneled catheters, peripherally inserted central catheters, and implanted ports.
- (a) For newly placed central lines, confirm tip placement prior to use. The central venous access tip should be located in the lower third of the superior vena cava or at or near the



cavoatrial junction (Infusion Nurses Society, 2021).

- (b) Prior to each use, always confirm that the implanted venous port tip is in the vascular system and not intraperitoneal or intra-arterial. Venous implanted ports are sometimes placed over a lower rib and may be incorrectly identified as intraperitoneal or intra-arterial.
- (c) Prior to administration of cancer therapy, assess for signs and symptoms of malposition or occlusion. Do not proceed and contact the provider if any of the following are present (Infusion Nurses Society, 2021):
  - i. Absent or sluggish blood return
  - ii. Change in color and or pulsatility of blood from lumens
  - iii. Difficulty flushing or IV does not flow freely off of the IV pump
  - iv. Atrial or ventricular arrhythmias
  - v. Pain, edema, or strange sensations in the neck, shoulder, chest, or back
  - vi. Gurgling or rushing sound on the side of the central venous access device, which could indicate tip malposition in the jugular vein
  - vii. New neurologic changes or paresthesias
- (d) Follow institutional guidelines for troubleshooting and declogging procedures and dye studies.
- (e) For implanted ports, access the port with a noncoring needle. Select the appropriate needle length based on the depth of the port. Stabilize the needle with tape and transparent dressing or a securement device to help prevent dislodgment and possible infiltration during medication administration. Inspect the insertion site for evidence of needle dislodgment, including absent or sluggish blood return, leakage of IV fluid, edema, and discomfort or pain.
- (f) For all central venous access devices, use a transparent dressing to ensure visualization of the site during administration. Gauze may be used

to stabilize the needle wings as long as the insertion site is not covered (Infusion Nurses Society, 2021).

- (4) IV push method
  - (a) Refer to institutional guidelines and drug references for the recommended rate of administration. In addition, consider the status of the veins or type of venous access.
  - (b) Although limited published evidence exists supporting the superiority of the side-arm technique method for IV push over other methods, the side-arm technique allows for constant dilution of vesicant during administration, which may decrease the severity of an extravasation injury.
  - (c) Side-arm technique for administration of IV push
    - i. Hang a mainline IV line with a solution compatible with the IV push medications.
    - ii. Allow the mainline IV solution to run freely without using an infusion pump.
    - iii. Prior to attaching the chemotherapy syringe, flush the IV line with a prefilled saline syringe (5–10 ml). Confirm blood return and flush to verify there are no signs or symptoms of infiltration.
    - iv. Attach the antineoplastic syringe to the injection port (Y-site) closest to the patient on the mainline IV tubing (e.g., 0.9% sodium chloride). A CSTD should be attached to the end of the syringe (Polovich & Olsen, 2018). Some systems require a CSTD adaptor attached to the Y-site on the mainline IV tubing.
    - v. Slowly administer the medication. Allow the mainline IV solution to run continuously during the IV push to dilute the medication. Do not pinch the mainline IV tubing while pushing the antineoplastic medication. Keep a thumb on the plunger of the syringe to prevent primary IV fluid from backing up into the syringe.

- vi. Assess for blood return every 2–5 ml. Blood return can be checked by slowly pulling back on the antineoplastic syringe.
  - vii. Continuously assess the site for signs and symptoms of infiltration or extravasation. Patency checks should include blood return, the appearance of the IV site, patient reports, and the ability of the primary IV to run freely off of the pump.
  - viii. If multiple medications are administered, flush with the mainline IV solution between each drug and after the infusion.
  - ix. Discontinue administration immediately for signs or symptoms of infiltration or extravasation. (e.g., pain, burning, redness, edema, leaking at IV site, any patient-reported discomfort). It is essential to distinguish between extravasation and flare reaction (see Chapter 13).
- (5) Intermittent/minibag infusion (IV piggyback)
- (a) Hang a mainline IV compatible with the medications to be administered.
  - (b) Flush the IV line with a prefilled saline syringe (5–10 ml). Use the injection port (Y-site) on the mainline IV tubing closest to the patient.
  - (c) Assess for blood return and other signs of patency (e.g., no pain, burning, redness, edema, leaking at IV site, any patient-reported discomfort).
  - (d) Nonvesicant short-term/minibag (IV piggyback) infusions
    - i. Insert the medication tubing into the Y-site above or below the IV pump, depending on the agent or institutional procedure. A CSTD should be attached to the end of the HD IV tubing. (Polovich & Olsen, 2018). Some systems require a CSTD adaptor attached to the Y-site on the mainline IV tubing.
    - ii. Infuse as ordered or per institutional guidelines or drug reference.
- iii. Assess for signs and symptoms of infiltration.
  - iv. If multiple agents are administered, flush with the mainline IV solution between each agent and after the infusion.
- (e) Vesicant short-term/minibag infusions
- i. Peripheral IV administration
    - Remain with the patient during the entire infusion, as extravasation is a risk for peripheral lines.
    - Use a transparent dressing to visualize the IV site.
    - A CSTD should be attached to the end of the HD IV tubing (Polovich & Olsen, 2018). Some systems require a CSTD adaptor attached to the Y-site on the mainline IV tubing.
    - Administer by gravity through a free-flowing mainline IV. Do not use an infusion pump to administer vesicants through a peripheral IV.
    - Limit administration to 30 minutes or less.
    - Infuse as ordered or per institutional guidelines or drug reference.
    - Verify blood return before, every five minutes during, and after the infusion is complete. Assess for signs and symptoms of infiltration.
    - If multiple agents are administered, flush with the mainline IV solution between each agent and after the infusion.
    - See Chapter 13 for more information on taxane administration.
  - ii. Central venous catheter administration
    - Remain with the patient during the entire infusion, as extravasation is a risk for central and peripheral lines.
    - Use a transparent dressing to visualize the central line site.

- Insert the medication tubing into the Y-site above or below the IV pump, depending on the agent or institutional procedure.
  - Limit administration to 30 minutes or less.
  - Infuse as ordered or per institutional guidelines or drug reference.
  - Verify blood return before, every five minutes during, and after the infusion is complete. Assess for signs and symptoms of infiltration.
  - If multiple agents are administered, flush with the mainline IV solution between each agent and after the infusion.
  - See Chapter 13 for more information on taxane administration.
- iii. Administer all vinca alkaloids as a short-term/minibag infusion (IV piggyback) (ISMP, 2016; NCCN, 2016; Neuss et al., 2016).
- iv. Studies have indicated the risk of extravasation is less than 0.05% when vinca alkaloids are administered using the following method (Gilbar & Carrington, 2006; Hartkopf-Smith & Hughes-McNally, 2012; Nurgat et al., 2015):
- Vinca alkaloids should be prepared as a minibag infusion (e.g., 25–50 ml).
  - Do not use an IV pump when administering vesicants through a peripheral IV.
  - Administer by gravity through a free-flowing primary IV line using a CSTD (Polovich & Olsen, 2018).
  - Remain with the patient during the entire infusion.
  - Use a transparent dressing to visualize the IV site.
  - Infuse over 5–15 minutes.
  - Assess for blood return during any vesicant administration via a short-term infusion before, every five minutes during, and after the infusion is complete.
  - Closely monitor for signs and symptoms of extravasation, such as swelling, loss of blood return, and patient-reported pain or burning sensation.
  - Discontinue administration immediately for signs and symptoms of infiltration and extravasation.
  - See Chapter 13 for management of vesicant extravasation.
- (6) Continuous infusions
- (a) Assess for blood return and other signs of patency prior to, during, and after drug administration according to institutional policy (e.g., pain, burning, redness, edema, leaking at the IV site, patient-reported discomfort).
- (b) Hang a mainline IV tubing with a solution compatible with the medications to be administered (excluding home infusions using ambulatory infusion pumps).
- (c) Use an IV pump. Administer via a programmable infusion pump using dose error-reduction software in inpatient and outpatient areas (ISMP, 2022).
- (d) Connect antineoplastic tubing into primary IV per institutional policy. Use a CSTD to administer HDs. Configure the mainline IV tubing and antineoplastic tubing so that the tubing does not need to be disconnected each time a blood return is checked. Use a CSTD for blood return checks to reduce exposure to HDs (Polovich & Olsen, 2018).
- (e) Infuse as ordered or per institutional guidelines or drug reference.
- (f) Assess for signs and symptoms of infiltration.
- (g) Continuous infusions of vesicants
- i. Always infuse through a central venous access device with positive blood return and tip location confirmed as central.
  - ii. Assess for blood return and other signs and symptoms of

extravasation prior to initiating the infusion, at periods specified by institutional policy (e.g., every four hours), and after the infusion.

- iii. Check for blood return and other signs and symptoms of extravasation if there are any indications that the pump is not flowing (e.g., pump alarm for occlusion, infusion rate appears to be too slow).
- iv. Use a transparent dressing over the site to visualize signs and symptoms of extravasation.
- v. Discontinue administration immediately for signs and symptoms of infiltration and extravasation. See Chapter 13 for management of vesicant extravasation.

#### 4. Intraperitoneal

a) Intraperitoneal chemotherapy is the administration of chemotherapy directly into the peritoneal cavity via an external catheter or port.

- (1) It is most frequently used for ovarian cancer, as the most common route of spread for this cancer is within the peritoneal cavity (NCCN, 2022d).
- (2) Compared with IV chemotherapy, intraperitoneal administration permits a several-fold increase in drug concentration within the abdominal cavity (Dedrick et al., 1978).
  - (a) Intraperitoneal therapy in conjunction with IV chemotherapy is indicated for patients with optimally debulked stage III and IV ovarian cancer (i.e., patients with no or minimal residual disease after surgical cytoreduction) (NCCN, 2022d).
  - (b) The penetration of chemotherapy into tumor tissue is limited to a few millimeters of tumor on the peritoneal surface layers (NCCN, 2022d).
- (3) The most commonly administered intraperitoneal agents for ovarian cancer are cisplatin and paclitaxel (NCCN, 2022d).

b) Pretreatment assessment (in addition to the general pretreatment assessment)

- (1) Verify the type of device (implanted intraperitoneal port vs. external intraperitoneal catheter) and catheter tip location in intraperitoneal space by reviewing operative notes or imaging.

(2) Assess for signs and symptoms of access device complications (Camp-Sorrell & Matey, 2017).

- (a) Exit site infection (e.g., fever, chills, drainage, erythema, tenderness at site)
- (b) Tunneled catheters (e.g., tunnel infection, inflammation appearing along the tunnel line)
- (c) Leakage, bleeding, drainage at the exit site
- (d) Presence or absence of ascites: If patients have ascites, discuss with the prescriber if ascites should be drained prior to chemotherapy to promote comfort and tolerance (Camp-Sorrell & Matey, 2017).

(3) Baseline respiratory status: Note any shortness of breath.

(4) Signs and symptoms of peritonitis (e.g., fever, chills, abdominal pain): If positive, notify the provider and anticipate orders for peritoneal fluid cultures.

- (a) Peritoneal fluid cultures may not be possible to draw if patients do not have ascites.
- (b) Peritonitis is diagnosed by confirming clinical features consistent with peritonitis (i.e., abdominal pain or cloudy dialysis effluent); dialysis effluent white cell count greater than 100/mm<sup>3</sup> (after a dwell time of at least two hours), with greater than 50% polymorphonuclear; and a positive dialysis effluent culture (Li et al., 2016).

(5) Abdominal pain, cramping, diarrhea

(6) Peripheral neuropathy from previous doses of platinum or taxane chemotherapy: Report any peripheral neuropathy. Intraperitoneal chemotherapy may be held for worsening peripheral neuropathy.

(7) Renal function: Check serum creatinine and creatinine clearance prior to cisplatin.

c) System safeguards to prevent errors and manage emergencies (see Chapters 1, 12, and 13)

- (1) Clearly label lines as intraperitoneal and IV to prevent accidental administration of medications via the incorrect route.
- (2) When administering medications and fluids, trace all catheters and lines from the access site into the patient's body.
- (3) Route IV tubing and intraperitoneal tubing to different sides of the bed or chair.

- (4) Infuse intraperitoneal fluids through tubing without injection ports (Y-sites) to prevent the accidental administration of IV medications (Camp-Sorrell & Matey, 2017).
  - (5) Intraperitoneal administration of paclitaxel and cisplatin can cause hypersensitivity reactions, including anaphylaxis. Ensure that emergency medications are available and that patients have patent venous access.
  - (6) Always have peripheral venous access in place for potential emergencies.
- d) Dosing: Intraperitoneal dosing is based on the disease, regimen, patient-specific factors, and presence of toxicities. Care must be taken to verify the dosing of intraperitoneal and IV chemotherapy when administered in the same regimen.
- e) Verification: Immediately prior to administration, verify that the agent to be administered is intraperitoneal and that the tubing and line it is connected to is the intraperitoneal access device (see section D).
- f) Administration
- (1) Ask patients to void prior to starting the procedure and to report difficulty with voiding or a lack of urine output.
  - (2) Obtain IV access for administration of IV fluids and premedications (e.g., prior to administration of intraperitoneal cisplatin).
  - (3) Access the intraperitoneal port.
    - (a) Apply topical anesthetic, if requested.
    - (b) Use a strict sterile technique and maximum barrier precautions when accessing an intraperitoneal port (Camp-Sorrell & Matey, 2017).
    - (c) Instruct patients to lie flat for port access, if possible.
    - (d) Use a noncoring needle. A longer needle may be needed (e.g., 1.5 in) due to the port's location.
    - (e) A blood return should not occur if aspiration is attempted, as the tip of the catheter is in the peritoneal space. If patients have ascites, peritoneal fluid may be withdrawn (often straw-colored, sometimes blood-tinged). Often, intraperitoneal ports will not yield a specimen (Camp-Sorrell & Matey, 2017).
    - (f) Flush with 10–20 ml normal saline. Assess for signs and symptoms of infiltration, including pain, burning, and leaking of fluid (Camp-Sorrell & Matey, 2017).
    - (g) Apply a sterile transparent dressing.
  - (4) Place patients in a semi-Fowler position. A flat position during infusion may increase pressure on the diaphragm, causing respiratory compromise and gastrointestinal upset.
  - (5) Administer IV premedications and hydration as ordered.
  - (6) No definitive recommendations can be made regarding the warming of intraperitoneal fluid prior to administration (Rogers et al., 2017).
    - (a) Patients may tolerate warmed or room-temperature fluids better than cold (BC Renal, 2018).
    - (b) If fluids are warmed, dry heat sources should be used (BC Renal, 2018). U.S. Food and Drug Administration–approved fluid warming cabinets are an example of dry heat.
    - (c) Water baths should not be used for heating solutions due to the potential of waterborne organism contamination to the system (BC Renal, 2018).
    - (d) Do not microwave fluids for intraperitoneal use. This can create “hot spots” and potential burns (BC Renal, 2018). Although intraperitoneal chemotherapy is not mixed in dialysis solution, manufacturers of peritoneal dialysis solutions do not recommend heating using a microwave (Baxter Healthcare, 2015). If intraperitoneal solutions are warmed, temperature regulation should ensure that solutions are heated to 37°C ( $\pm 0.5^\circ\text{C}$ ) (BC Renal, 2018).
    - (e) If fluids are warmed with dry heat, it should be used as soon as possible once removed from the warmer. Fluids should not be exposed to a heat source for an extended period. Extended heating can lead to a breakdown of dextrose, leading to a brown color (BC Renal, 2018).
  - (7) Wear personal protective (PPE) equipment, which includes a gown tested for use with chemotherapy. If unavailable, use a lint-free gown made of a low-permeability fabric, such as polypropylene or other laminate materials, and two pair of gloves tested for use with HDs. Mask and face protection should also be used.

- (8) Chemotherapy is often mixed in one liter of fluid followed by an additional liter of normal saline. If the patient experiences discomfort and fullness, the second liter of intraperitoneal fluid (normal saline) is often discontinued (Anastasia, 2012).
- (9) Infuse intraperitoneal fluids by gravity as rapidly as the patient will tolerate (Anastasia, 2012; Potter & Held-Warmkessel, 2008).
  - (a) Do not use an IV pump, as it has been associated with needle dislodgment and infiltration (Potter & Held-Warmkessel, 2008).
  - (b) Do not use a pressure bag to infuse fluids through an intraperitoneal port.
  - (c) The fluid should flow freely and is often infused over 60–180 minutes. If the infusion will not run within this period, notify the prescriber, as the catheter may be malpositioned, have a fibrin sheath, or the tip may be located in a pocket formed from bowel adhesions in the intraperitoneal cavity (Anastasia, 2012; Camp-Sorrell & Matey, 2017; Potter & Held-Warmkessel, 2008). Check for port needle dislodgment.
  - (d) Slow the intraperitoneal infusion for complaints of abdominal discomfort, cramping, or dyspnea (Anastasia, 2012; Camp-Sorrell & Matey, 2017; Potter & Held-Warmkessel, 2008).
  - (e) Discontinue the infusion for signs and symptoms of infiltration at the port site.
- (10) Although commonly implemented, no evidence supports patient turning.
- (11) When the infusion is complete, disconnect the tubing. Flush with a minimum of 20 ml normal saline and discontinue the port needle. No definitive recommendations can be made regarding the use of heparin (Camp-Sorrell & Matey, 2017).
- (12) The infused fluid is not drained and will absorb over several days to a week (Potter & Held-Warmkessel, 2008).
- (13) Assess for the following throughout the intraperitoneal infusion and after completion (Anastasia, 2012; Camp-Sorrell & Matey, 2017; Potter & Held-Warmkessel, 2008):
  - (a) Signs and symptoms of a hypersensitivity reaction
    - (b) Signs and symptoms of fluid overload
    - (c) Dyspnea
    - (d) Abdominal pain or discomfort
    - (e) Failure of the intraperitoneal fluids to infuse freely by gravity (Anastasia, 2012; Camp-Sorrell & Matey, 2017)
      - i. Line placement and patency may need to be confirmed by a dye study with fluoroscopy.
      - ii. The procedure may indicate complications such as adhesions, retrograde dye flow along the catheter into the port pocket (due to a fibrin sheath), and dye entering the gastrointestinal tract (Markman & Olawaiye, 2021).
    - (f) Leaking around the port needle site or external catheter exit site (Anastasia, 2012; Camp-Sorrell & Matey, 2017)
      - i. Verify needle placement.
      - ii. Excessive pressure from ascites can cause leaking around the catheter or needle.
    - (g) In the event of extravasation (evidenced by abdominal pain and delayed erythema, often due to port malfunction or flipping) or intraperitoneal port malfunction, discontinue intraperitoneal therapy and notify the authorized prescriber immediately.
    - (h) For patients on cisplatin, monitor magnesium levels, and administer replacement as ordered.
    - (i) For patients with significant nausea or vomiting who cannot self-hydrate, consider scheduling return visits for IV hydration.
- g) Other considerations
  - (1) Heated intraperitoneal chemotherapy (HIPEC) is the intraoperative delivery of heated chemotherapy into the intraperitoneal space. It is administered following cytoreductive surgery to eradicate microscopic disease. Hyperthermia is used to increase the uptake of chemotherapy into cancer cells (Goodman et al., 2016).
  - (2) HIPEC has been used for various intraperitoneal cancers, including appendiceal, ovarian, peritoneal mesothelioma, and colon cancer (Goodman et al., 2016).
  - (3) Agents used during HIPEC include carboplatin, cisplatin, 5-fluorouracil, irinotecan,



mitomycin C, and oxaliplatin (Goodman et al., 2016).

- (4) The HIPEC procedure is performed after the cytoreductive surgery. The surgeon places intraperitoneal catheters and temperature probes into the intraperitoneal space. The chemotherapy is heated by a perfusion machine and continuously circulates throughout the intraperitoneal cavity, often for two hours.
  - (5) All personnel who administer HDs via the intraperitoneal route must wear two pairs of gloves tested for use with HDs. Personnel must also wear a gown during IV administration and a mask with face protection if the potential for spilling, splashing, or aerosols exists (Polovich & Olsen, 2018; see Chapter 12).
  - (6) Patients are often rocked back and forth during the procedure. After the procedure, the chemotherapy is drained, and the catheters are removed.
  - (7) Patients are then transferred to the intensive care unit and usually hospitalized until recovery.
  - (8) Complications from the procedure include nausea, vomiting, pain, bleeding, ileus, anastomotic leaks, bowel perforations, and infection (Piso et al., 2019).
  - (9) In many institutions, perfusionists in surgery work with the surgeon to administer HIPEC. Although nurses do not administer the chemotherapy intraoperatively, they play an important role in preventing and managing related complications.
5. Intrathecal via lumbar puncture
- a) Intrathecal chemotherapy is the administration of chemotherapy directly into the intrathecal space by a lumbar puncture. The goal of intrathecal chemotherapy is the prophylaxis or treatment of malignant cells within sites that cannot be reached by systemic chemotherapy because of the blood–brain barrier (NCCN, 2021a, 2021b, 2022a).
    - (1) Indications for prophylactic intrathecal chemotherapy include acute lymphoblastic leukemia (NCCN, 2022a) and Burkitt lymphoma (NCCN, 2021b).
    - (2) Intrathecal chemotherapy is also used for leptomeningeal metastasis (meningeal carcinomatosis) that can occur from the spread of leukemia, lymphoma, and solid tumors, such as breast, lung, and gastrointestinal cancers (NCCN, 2021a, 2021b, 2021f, 2022a).
      - (a) The leptomeninges are two tissue linings, the arachnoid and pia mater, covering the brain and spinal cord. The layers encase the arachnoid space, which contains cerebrospinal fluid.
      - (b) Cancer cells can enter the cerebrospinal fluid by numerous routes, including the blood, the meninges, and extension from spinal metastases.
  - (3) Few chemotherapy agents can safely be given into the intrathecal space. The most commonly used agents are cytarabine and methotrexate (Gabay et al., 2012).
  - b) Pretreatment assessment (in addition to the general pretreatment assessment)
    - (1) Assess the patient's risk for bleeding. Increased bleeding increases the risk of an epidural hematoma and possible paralysis from the lumbar puncture (Balaban et al., 2016; Nair, 2016).
      - (a) Review the patient's laboratory values for bleeding risk (e.g., platelets, coagulation studies) and follow institutional guidelines. Many institutional guidelines are extrapolated from epidural guidelines. Dodd et al. (2018) developed guidelines specifically for lumbar puncture.
      - (b) Review the medication list. Determine if the patient has been on any anticoagulants or nonsteroidal anti-inflammatory drugs.
        - i. Obtain information regarding the dose, route, date, and time of the last administration.
        - ii. The American Society of Regional Anesthesia and Pain Medicine, European Society of Regional Anaesthesia and Pain Therapy, American Academy of Pain Medicine, International Neuromodulation Society, North American Neuro-modulation Society, and World Institute of Pain have established guidelines for procedures involving the spine (e.g., lumbar puncture) for patients on antiplatelet and anticoagulant medications (Narouze et al., 2018). The guidelines include specific details about when anticoagulants should be held and restarted concerning a lumbar puncture.

- (2) Review if the patient has any abnormalities of the lumbar vertebrae or would have difficulty maintaining the position required for the procedure.
  - (3) Clarify whether cerebrospinal fluid specimens should be drawn and sent to the prescriber (e.g., cytology, cell count, glucose, protein, biomarkers).
  - (4) Conduct a neurologic assessment to establish baseline orientation, level of consciousness, presence or absence of headaches, history of seizures, and numbness, tingling, or pain in lower extremities.
- c) System safeguards to prevent errors and manage emergencies: This section applies to both the intrathecal and intraventricular routes (see Chapters 1, 12, and 13).
- (1) Establish institutional policies and procedures related to anticoagulants, coagulation studies, and lumbar puncture.
  - (2) Work with an interprofessional team to prevent fatal chemotherapy errors related to the inadvertent administration of vinca alkaloids into the cerebrospinal fluid (Clement & Holle, 2017; Hartkopf Smith, 2009b; ISMP, 2020b). The institution should establish policies and procedures for intrathecal chemotherapy that radiologists give in interventional radiology or other radiology areas, as personnel in these areas are typically not familiar with the safe handling of HDs and the required safety checks prior to administration (Clement & Holle, 2017; Hartkopf Smith, 2009a).
    - (a) Since the approval of vincristine in the 1960s, more than 125 deaths have been reported from the accidental administration of vinca alkaloids into the intrathecal space (ISMP, 2020b; NCCN, 2016).
    - (b) Many patients receive IV vincristine as part of their chemotherapy regimen, including chemotherapy given into the intrathecal or intraventricular space. In most reports of accidental intrathecal administration, the syringe of vincristine was accidentally administered into the cerebrospinal fluid instead of the intended medication.
    - (c) Administration of vinca alkaloids, such as vincristine, given via this route can cause severe neurologic toxicity, including coma and death (ISMP, 2020b; Reddy et al., 2011).
- (d) More than 20 years ago, the U.S. Pharmacopeial Convention developed requirements for manufacturers and pharmacies to label doses of vincristine with warnings (Schulmeister, 2007). However, accidental injection of vincristine, vinblastine, vinorelbine, and bortezomib continues to occur. The U.S. Food and Drug Administration (2022) updated vinca alkaloid labeling for preparation in IV infusion bags only.
- (e) Strategies to prevent errors (ISMP, 2020b; NCCN, 2016)
- i. Vincristine and other vinca alkaloids must only be given via IV in a minibag (e.g., IV piggyback).
  - ii. Never dispense vinca alkaloids to an area where intrathecal or intraventricular medications are administered.
  - iii. Never give vinca alkaloids in the same treatment room as intrathecal or intraventricular medications.
  - iv. Healthcare providers who prescribe, prepare, and administer intrathecal or intraventricular chemotherapy must receive specialized educational programs that include the safe handling of HDs.
  - v. Institutions should establish a list of drugs that can be given intrathecally or intraventricularly.
  - vi. Orders for intrathecal chemotherapy should be separate from IV chemotherapy orders.
  - vii. Order and deliver intrathecal or intraventricular chemotherapy as close as possible to the time of administration.
  - viii. Package and transport intrathecal and intraventricular chemotherapy separately from IV and other drugs.
  - ix. Intrathecal and intraventricular chemotherapy should not be stored in patient care areas.
  - x. Time-out procedures should be conducted immediately preceding intrathecal and intraventricular chemotherapy administration.



- d) Dosing: A agent may be administered up to three times a week, depending on the regimen. The duration and frequency of treatment often depend on whether the goal is prophylaxis or treatment.
- e) Verification (see section D)
- (1) Verify that the patient's coagulation studies meet institutional parameters for a lumbar puncture.
  - (2) Verify that the patient is not receiving anticoagulants or that they have been discontinued for the necessary amount of time before the lumbar puncture per institutional standards.
  - (3) Immediately preceding the procedure
    - (a) Perform a time-out procedure.
    - (b) Verify with the practitioner performing the procedure (e.g., oncologist, radiologist, advanced practice provider) the following information:
      - i. The medication to be administered is safe via the intrathecal route.
      - ii. The medication is not a vinca alkaloid or bortezomib.
      - iii. The medication is mixed with preservative-free normal saline.
- f) Administration
- (1) Intrathecal chemotherapy via a lumbar puncture may be administered at the bedside, at an ambulatory care center, during interventional radiology, or with fluoroscopy, depending on the healthcare setting.
  - (2) It may be administered by an oncology physician, a radiologist, an advanced practice provider, or a physician assistant. Refer to state and institutional policies regarding the role of advanced practice nurses in administering intrathecal chemotherapy by a lumbar puncture.
  - (3) All personnel who administer HDs via this route must wear two pairs of gloves tested for use with HDs (outer gloves are sterile), a gown, and a mask with face protection (see Chapter 12). A plastic-backed absorbent pad should be placed under the site where the needle enters the spine and the syringe connection (Polovich & Olsen, 2018).
  - (4) Use strict sterile technique and sterile barrier precautions (e.g., mask, sterile field, sterile gloves).
    - (a) A mask also decreases the transfer of *Streptococcus salivarius* bacteria that can cause meningitis to the treatment field (Shewmaker et al., 2010).
- (b) Position the patient in the lateral recumbent or prone positions or sitting upright. The lateral recumbent or prone positions are preferred over the upright position because they allow a more accurate measurement of the opening pressure (Johnson & Sexton, 2021). The prone position is generally used for lumbar punctures performed under fluoroscopic guidance (Johnson & Sexton, 2021).
- (c) Cleanse the skin prior to needle puncture with an antiseptic and let dry completely to ensure that it adequately kills organisms and does not enter the cerebrospinal fluid. Refer to the type of antiseptic to determine the duration of the scrub and dry time.
- i. The choice of antiseptic is controversial (Al Dweikat, 2020).
  - ii. Current package labeling for chlorhexidine gluconate states to avoid contact with the meninges (i.e., do not use on lumbar puncture sites) due to reports of meningitis (Lexicomp, 2021a; Sviggum et al., 2012).
  - iii. Proponents of chlorhexidine use over povidone-iodine cite a more rapid onset of action, extended duration of effect, rare drug resistance, and little evidence to support its role in developing meningitis (Al Dweikat, 2020; Sviggum et al., 2012).
- (d) If the outside of the chemotherapy syringe is not sterile when dispensed, special procedures must be followed to maintain sterility during lumbar puncture (Aiello-Laws & Rutledge, 2008; Elledge, 2017). If the syringe containing the medication is sterile, the label on the medication must also be sterile (Aiello-Laws & Rutledge, 2008). For nonsterile syringes, the provider should access the cerebrospinal fluid with sterile gloves and administer intrathecal medication without touching the sterile access site (Polovich & Olsen, 2018).

- (e) The needle and infusion syringe and tubing should be discarded in an appropriate HD container (Polovich & Olsen, 2018).
- g) Other considerations: Post-lumbar puncture headache is a common complication of lumbar punctures and has been observed in 3.5%–33% of patients (Cognat et al., 2021). It is characterized by a headache that appears when the patient is in a standing position and resolves with lying down. Intracranial hypotension occurs due to a leakage of cerebrospinal fluid through a tear in the meninges. A systematic review assessed the efficacy of prolonged bedrest versus immediate ambulation and found a lack of evidence to support routine bedrest after lumbar puncture (Cognat et al., 2021). In addition, the use of atraumatic, noncutting needles was found to be the most effective intervention for post-lumbar puncture headache prevention (Cognat et al., 2021).
- 6. Intraventricular (e.g., Ommaya reservoir)
  - a) Intraventricular chemotherapy is the administration of chemotherapy into the lateral ventricle of the brain—a network of communicating cavities filled with cerebrospinal fluid.
    - (1) Intraventricular administration is an alternative to administering intrathecal chemotherapy by lumbar puncture and has the advantage of ease of access for repeated chemotherapy administration and cerebrospinal fluid blood sampling.
    - (2) Disadvantages include the need for surgical placement of the catheter, possible body image concerns, risk for infection, and catheter malposition (Wilson et al., 2018).
      - (a) Administration of vinca alkaloids, such as vincristine, given via this route can cause severe neurologic toxicity, including coma and death (Reddy et al., 2011).
      - (b) Ventricular reservoirs (Ommaya reservoirs) consist of a silicone dome and catheter. A neurosurgeon surgically places the dome under the scalp (SC), and the catheter is threaded into the lateral ventricle of the brain (Volkov et al., 2017).
        - i. The reservoir volume of the dome is 1.5–2.5 ml (Elledge, 2017). The catheter length varies, as it is trimmed to fit within the frontal horn of the lateral ventricle of the brain (Elledge, 2017).
        - ii. Ventricular reservoirs can be used to administer medications (i.e., chemotherapy) and sample cerebrospinal fluid.
        - iii. Some ventricular reservoirs have an attached shunt with an on-off flushing reservoir. Finger pressure on a specific device component can open and close the shunting system, thus controlling the flow of cerebrospinal fluid (Palejwala et al., 2014; Volkov et al., 2017). These reservoirs drain cerebrospinal fluid, usually into the peritoneal space. When chemotherapy is administered, the shunting system is closed. After a set time (e.g., four hours), the shunt is reopened (Volkov et al., 2017). These recommendations do not address the administration and management of patients with ventricular reservoirs with an attached shunt with on-off flushing reservoirs.
  - b) Pretreatment assessment (in addition to the general pretreatment assessment)
    - (1) Prior to accessing and using a ventricular reservoir, verify it is within scope of practice by the state board of nursing and institutional policy.
    - (2) Confirm that postoperative imaging was completed to confirm reservoir placement (e.g., magnetic resonance imaging, computed tomography scan), flow patency, and cerebrospinal fluid flow (as indicated) (Elledge, 2017). Flow studies identify areas of obstruction that could prevent chemotherapy from being distributed equally, with resultant increased toxicity and decreased efficacy.
    - (3) Discuss with the provider when the ventricular access can be used. Practices vary from the day of placement to multiple days after placement (Elledge, 2017).
    - (4) Verify the type of ventricular access. Although typically called Ommayas (after its inventor Ayub Ommaya), various manufacturers make ventricular reservoirs, and the products are named differently. The different types of ventricular reservoirs can vary in reservoir volume.

- (5) Ensure that consent has been completed per institutional guidelines (see Chapter 2).
- (6) Assess laboratory values, including a complete blood count and differential. Discuss with the provider any altered coagulation values. The small gauge needle used typically causes minimal bleeding in patients with thrombocytopenia.
- (7) Clarify whether specimens should be drawn and sent to the prescriber (e.g., cytology, cell count, glucose, protein, biomarkers).
- (8) Clip (do not shave) the hair over the ventricular reservoir.
- (9) Assess vital signs.
- (10) Assess neurologic history and status to serve as a baseline, including but not limited to orientation, level of consciousness, headaches, and seizures.
- (11) Assess for signs of infection over the ventricular reservoir.
- c) System safeguards to prevent errors and manage emergencies: Follow system safeguards listed for the intrathecal route (refer to 5c; see Chapters 1, 12, and 13).
- d) Dosing: An agent may be administered up to three times a week, depending on the regimen. The duration and frequency of treatment often depend on whether the goal is prophylaxis or treatment.
- e) Verification (see section D)
  - (1) Perform the time-out procedure and pretreatment verification listed in section D.
  - (2) Verify the following information with another nurse deemed competent to administer antineoplastic therapy, a pharmacist, or a physician:
    - (a) The medication to be administered is safe via the intraventricular route.
    - (b) The medication is not a vinca alkaloid or bortezomib.
    - (c) The medication is mixed with preservative-free normal saline.
- f) Administration
  - (1) No consensus can be made regarding the patient's position during the procedure.
  - (2) All personnel who administer HDs via this route must wear two pairs of gloves tested for use with HDs (outer gloves are sterile), a gown, and a mask with face protection (see Chapter 12).
  - (3) Use strict sterile technique and sterile barrier precautions (e.g., mask, sterile field, sterile gloves).
    - (a) A mask also decreases the transfer of *Streptococcus salivarius* bacteria that can cause meningitis to the treatment field (Shewmaker et al., 2010).
    - (b) If the outside of the chemotherapy syringe is not sterile when dispensed, special procedures must be followed to maintain sterility during lumbar puncture (Aiello-Laws & Rutledge, 2008; Elledge, 2017). If the syringe containing the medication is sterile, the label on the medication must also be sterile (Aiello-Laws & Rutledge, 2008). For nonsterile syringes, the provider should access the cerebrospinal fluid with sterile gloves and administer intrathecal medication without touching the sterile access site (Polovich & Olsen, 2018).
  - (4) Cleanse the reservoir prior to needle puncture with an antiseptic and let dry completely to ensure that it adequately kills organisms and does not enter the cerebrospinal fluid. Refer to the type of antiseptic to determine the duration of the scrub and dry time.
    - (a) Current package labeling for chlorhexidine gluconate states to avoid contact with the meninges (i.e., do not use on lumbar puncture sites) due to reports of meningitis (Lexi-comp, 2021a; Sviggum et al., 2012).
    - (b) Proponents of chlorhexidine use over povidone-iodine cite a more rapid onset of action, extended duration of effect, rare drug resistance, and little evidence to support its role in developing meningitis (Al Dweikat, 2020; Sviggum et al., 2012).
  - (5) Use a 25-gauge or smaller butterfly needle and attach extension tubing to an empty syringe (equal to the volume of the chemotherapy syringe) (Aiello-Laws & Rutledge, 2008; Elledge, 2017; Integra Life-Sciences, 2014).
  - (6) Some practices recommend using a stopcock, with the empty syringe for aspiration and the chemotherapy syringe attached to different ports of the stopcock. The stopcock is connected to the tubing on the butterfly needle. Never use a vacutainer (Aiello-Laws & Rutledge, 2008).
  - (7) Palpate the reservoir.
  - (8) Insert the butterfly at a 90° angle into the ventricular reservoir. Once it is inside the

- dome of the reservoir, decreased resistance should be felt.
- (9) Slowly aspirate. If blood is present, stop and withdraw the needle. If blood is not present, slowly withdraw cerebrospinal fluid equal to the volume of chemotherapy to be administered (Aiello-Laws & Rutledge, 2008; Elledge, 2017).
  - (10) Examine the cerebrospinal fluid. If it is cloudy or bloody, do not proceed with chemotherapy until you have discussed the findings with the provider. Anticipate orders to send a specimen for testing. Proceed if the cerebral spinal fluid is clear.
  - (11) Disconnect the syringe with cerebrospinal fluid (pinch tubing or close the stopcock first). Save the cerebrospinal fluid syringe if specimens are ordered or indicated. Attach the chemotherapy syringe (unpinch tubing or open the stopcock to the chemotherapy syringe) and slowly administer the chemotherapy.
  - (12) Flush with preservative-free normal saline (Aiello-Laws & Rutledge, 2008; Camp-Sorrell & Matey, 2017).
  - (13) Remove the needle.
  - (14) Apply pressure with sterile gauze.
  - (15) Apply a sterile dressing.
  - (16) Postprocedure care
    - (a) No consensus can be made regarding the patient's position following the procedure.
    - (b) Take vital signs.
    - (c) Assess for complications, including headaches, nausea, vomiting, seizures, and changes in neurologic status.
      - i. Acute neurotoxicity due to intrathecal chemotherapy can present within 24–48 hours as chemical arachnoiditis with headache, nuchal rigidity, back pain, vomiting, fever, and seizures (Jacob et al., 2015).
      - ii. Catheter migration or location too close to a vital structure can cause neurologic symptoms, such as headaches, seizures, and nausea, during or immediately after the procedure (Mauler et al., 2020). A computed tomography scan, magnetic resonance imaging, or flow study can help rule out catheter migration.
- (d) If specimens are ordered, label and send per institutional policy and procedure.
- g) Patient education
    - (1) Instruct patients to notify the healthcare provider if headache, nausea, vomiting, neck stiffness, or other neurologic symptoms develop.
    - (2) Instruct patients to avoid trauma to the ventricular reservoir site.
- ## 7. Intravesical (bladder)
- a) Intravesical chemotherapy is the regional administration of chemotherapy directly into the bladder. The medication is administered through a catheter and can be done intraoperatively, immediately postoperatively, and weekly in the outpatient area.
    - (1) Indications include superficial, nonmuscle invasive bladder cancer and selected patients who are not candidates for cystectomy (NCCN, 2022b).
    - (2) Commonly used agents include bacillus Calmette-Guérin (BCG), docetaxel, epirubicin, gemcitabine, mitomycin C, and valrubicin (NCCN, 2022b).
    - (3) BCG contains live attenuated mycobacteria. Because of the potential risk for transmission, it should be prepared, handled, and disposed of as a biohazard material (National Institute for Occupational Safety and Health [NIOSH], 2016). BCG preparation is performed using sterile technique and is not prepared in areas where other parenteral medications are prepared (NIOSH, 2016). BCG treatment contains live bacteria. Patients are instructed to not use public toilets for six hours after treatment and to sit down on the toilet to avoid splashing. They should add 2 cups of undiluted bleach to the toilet, close the lid, and wait 15 minutes before flushing. These precautions may prove difficult to maintain in a busy oncology infusion clinic, and risk to other patients should be considered if implementing this treatment outside of a urology clinic.
    - (4) Intravesical chemotherapy is sometimes given sequentially on the same day (Steinberg et al., 2015). The first medication is instilled and left in for a designated dwell time. The medication is then drained, the catheter flushed with normal saline, and a second medication is instilled, held for a designated dwell time, and then drained.

b) Pretreatment assessment (in addition to the general pretreatment assessment)

- (1) Measure baseline vital signs.
- (2) Verify any allergies to latex, tape, and antiseptic.
- (3) Review medications, as some antibiotics (e.g., fluoroquinolones) may decrease the effectiveness of BCG (Lexicomp, 2021b).
- (4) Treatment is contraindicated in women who are pregnant or breastfeeding.
- (5) If signs and symptoms of a bladder infection (e.g., fever, burning, urgency, frequency, gross hematuria) are present, hold treatment and notify the provider. A routine screening urinalysis is no longer included in the American Urological Association and Society of Urologic Nurses and Associates (2020) guidelines for intravesical treatments. Send a urine culture as ordered. Discuss results with the provider.
- (6) An anticholinergic may be given before the procedure for patients with a history of bladder spasms.
- (7) A special catheter or topical anesthetic may be indicated for patients with a history of difficult or painful catheterization.
- (8) Assess for signs and symptoms of urinary frequency and inability to hold urine.
- (9) Because BCG is a live attenuated form of *Mycobacterium tuberculosis*, assess for the following contraindications to treatment (American Urological Association & Society of Urologic Nurses and Associates, 2020):
  - (a) Within 14 days following bladder or prostatic surgery, including biopsy
  - (b) Within 14 days following traumatic catheterization
  - (c) Traumatic catheterization or gross hematuria on the day of treatment
  - (d) Active tuberculosis: Lexicomp (2021b) recommends a purified protein derivative (PPD) test prior to starting BCG therapy. Patients with a positive PPD test should be further assessed for signs and symptoms of active or latent tuberculosis. The American Urological Association and Society of Urologic Nurses and Associates (2020) guidelines do not include a PPD test as part of the pretreatment assessment.
  - (e) Immunosuppressed patients with congenital or acquired immune defi-

ciency, whether due to concurrent disease (e.g., AIDS, leukemia, lymphoma), cancer therapy (e.g., cytotoxic drugs, radiation), or immunosuppressive therapy (e.g., corticosteroids)

- (f) Symptomatic urinary tract infection
- (g) Fever

c) System safeguards to prevent errors and manage emergencies (also see Chapters 1, 12, and 13)

d) Dosing: The dosing, duration, and frequency are dependent on individual patient factors and the regimens prescribed. The dosing of the different brands of intravesical BCG vary.

e) Verification (see section D)

f) Administration (American Urological Association & Society of Urologic Nurses and Associates, 2020; Hartkopf-Smith, 2020)

- (1) For postoperative patients, obtain an order to discontinue any continuous bladder irrigation for a minimum of one hour before treatment.
- (2) Wear PPE, which includes a gown tested for use with chemotherapy. If unavailable, use a lint-free gown made of a low-permeability fabric, such as polypropylene or other laminate materials, and two pair of gloves tested for use with chemotherapy. Mask and face protection should also be used.
- (3) Place the patient in a supine position and place a plastic-backed pad under the patient's hips.
- (4) If the patient has had difficult or painful catheterizations in the past, apply a topical anesthetic as ordered.
- (5) Using a sterile technique, place a urethral catheter and completely drain the bladder.
  - (a) Using a Foley catheter with an attached drainage bag is preferred, as it allows for a closed system for administration and drainage and prevents spills of HDs. Ensure that the Foley tubing has a port compatible with the CSTD on the end of the syringe or chemotherapy tubing.
  - (b) A straight catheter with a CSTD adaptor can be used if the patient can hold their urine for the designated dwell time without leaking and a bathroom for single use during treatment is close.
    - i. After draining urine, place a CSTD catheter adaptor at the end of the catheter. The slip tip fits into the end of the catheter.



- ter. A cap is attached to the slip tip. The CSTD at the end of the medication syringe or tubing can be attached to the cap on the adaptor for bladder instillation of HDs.
- ii. If BCG is given, the patient's bathroom must be closed for 15 minutes after the patient voids. Two cups of bleach are placed in the toilet and must remain there for 15 minutes to effectively kill BCG.
- (6) Medications may be mixed in a Luer lock syringe or an IV bag with attached short tubing. Some medications (e.g., valrubicin) come with tubing; however, these may not be compatible with CSTDs. Assess to determine if a short IV tubing can be used instead.
  - (7) Syringes or IV tubings should have an attached CSTD.
  - (8) Inject or infuse the chemotherapy or immunotherapy at the prescribed rate. Slow the injection or infusion if the patient reports discomfort or bladder spasms. If using a Foley catheter, the tubing should be clamped (using a smooth clamp) so that the medication does not drain into the Foley bag during the dwell time. If using a straight catheter, the catheter and CSTD adaptor with cap should remain in place.
  - (9) Instruct the patient to hold the medication and not void for one to two hours (American Urological Association & Society of Urologic Nurses and Associates, 2020).
  - (10) No evidence supports having the patient turn from side to side and then lie on their back to ensure the medication comes in contact with the bladder (American Urological Association & Society of Urologic Nurses and Associates, 2020).
  - (11) After one to two hours, the medication may be drained.
    - (a) If the patient has a Foley catheter in place, unclamp the tubing and let the urine and medication drain into the bag. Remove the catheter with the attached bag. Always use safe handling precautions.
    - (b) If the patient has a straight catheter in place, remove it using a plastic-backed absorbent pad under the area in case of leakage. The patient can then void.
    - (c) Instruct male patients to sit while voiding for six hours following the administration of the agent. This prevents splashing of the medication (American Urological Association & Society of Urologic Nurses and Associates, 2020).
  - (12) Assess for pain, burning, spasms, and difficulty retaining urine for two hours. A rare side effect is extravasation during the administration of a vesicant agent, which can result in severe pelvic pain (Elmamoun et al., 2014; Nieuwenhuijzen et al., 2003).
  - (13) Dispose of items, including the catheter, in a designated HD container. If a Foley catheter and drainage bag were used, contain the entire intact urinary drainage system in sealable bags and place it in the designated HD container.
- g) Patient education (American Urological Association & Society of Urologic Nurses and Associates, 2020)
- (1) Restrict intake of fluid, caffeine, and diuretics beginning four hours before the procedure.
  - (2) Following the procedure
    - (a) Sit when voiding for six hours following the procedure to prevent splashing.
    - (b) Avoid using public toilets. Do not void outside.
    - (c) Increase fluid to dilute the urine.
    - (d) Wash any splashing on skin with soap and water. Wash glans or perineum after voiding.
    - (e) Wear a condom during intercourse until therapy is completed.
    - (f) For BCG, place two cups of bleach in the toilet after each void for six hours following the procedure. Let the bleach sit in the toilet for 15 minutes. Cover the toilet, and flush twice.
    - (g) Common side effects include low-grade fever, urinary frequency and urgency, bladder spasms, burning with urination, and fatigue.
    - (h) Remove clothes if contaminated with urine and wash separately.
8. Percutaneous nephrostomy infusions (e.g., renal pelvis, ureters)
- a) Percutaneous nephrostomy infusion is the regional administration of chemotherapy or immunotherapy directly into the renal pelvis or ureter using a nephrostomy tube or other percutaneous catheter. The medication is adminis-

tered through a catheter and can be given in the outpatient area.

- (1) The role of immunotherapy and chemotherapy for upper urinary tract cancer is not firmly established; however, the most established practice is the treatment of carcinoma in situ or small solitary tumors that are completely resected (Carmignani et al., 2013; Metcalf & Pierorazio, 2020).
  - (2) The most commonly used agents include BCG and mitomycin C (Metcalf & Pierorazio, 2020).
  - (3) BCG contains live attenuated mycobacteria. Because of the potential risk for transmission, it should be prepared, handled, and disposed of as a biohazard material (NIOSH, 2016).
- b) Pretreatment assessment (in addition to the general pretreatment assessment)
- (1) The location of the tip of the catheter should be documented in the patient's chart. Check the operative or radiology report.
  - (2) Assess the nephrostomy tube for kinks, tears, or leaks. The nephrostomy tube may have a cap (e.g., needleless connector) on the end rather than a bag.
  - (3) Check for nephrostomy tube patency by flushing with 10 ml normal saline. Do not proceed and notify the provider if resistance is met.
  - (4) Assess for urinary incontinence. If the patient reports incontinence, consider placing a Foley catheter, as the medication will be voided after the procedure.
  - (5) Assess for signs and symptoms of infection.
    - (a) Assess vital signs, including temperature.
    - (b) Check the nephrostomy tube exit site for redness, swelling, and drainage.
    - (c) Check for signs and symptoms of urinary tract infection.
    - (d) If an infection is suspected, do not proceed and notify the provider.
    - (e) Send a urine culture as ordered. Some providers will order a urine culture and IV antibiotic prior to each treatment (Herr, 1985).
  - (6) Medications. Some antibiotics (e.g., fluoroquinolones) may decrease the effectiveness of BCG (Lexicomp, 2021b).
  - (7) Because BCG is a live attenuated form of tuberculosis and some of the BCG drains into the bladder, assess for the following contraindications to treatment (American Urological Association & Society of Urologic Nurses and Associates, 2020; Lexicomp, 2021b):
    - (a) Within 14 days following bladder or prostatic surgery, including biopsy
    - (b) Within 14 days following traumatic catheterization
    - (c) Traumatic catheterization or gross hematuria on the day of treatment
    - (d) Active tuberculosis: Lexicomp (2021b) recommends a PPD test prior to starting BCG therapy. Patients with a positive PPD test should be further assessed for signs and symptoms of active or latent tuberculosis. The American Urological Association and Society of Urologic Nurses and Associates (2020) guidelines do not include a PPD test as part of the pretreatment assessment.
    - (e) Immunosuppressed patients with congenital or acquired immune deficiency, whether due to concurrent disease (e.g., AIDS, leukemia, lymphoma), cancer therapy (e.g., cytotoxic drugs, radiation), or immunosuppressive therapy (e.g., corticosteroids)
  - (8) Instruct the patient to void before and not during the procedure.
- c) System safeguards to prevent errors and manage emergencies (see Chapters 1, 12, and 13)
- (1) Clearly label lines as nephrostomy tube and IV (if ordered for an antibiotic) to prevent accidental administration of medications via the wrong route.
  - (2) When administering medications and fluids, trace all catheters and lines from the access site into the patient's body.
  - (3) Route IV tubing and nephrostomy tubing to different sides of the bed or chair.
  - (4) Infuse nephrostomy tube fluids through IV tubing without injection ports.
- d) Dosing: The dosing, duration, and frequency are dependent on individual patient factors and the regimens prescribed.
- e) Verification: Verify the location of the catheter tip by reviewing imaging or operative reports. Confirm that the catheter is in the ureter or renal pelvis (see section D).
- f) Administration
- (1) Detailed evidence-based information regarding administration is scarce in the literature.



- (a) In 1985, the first case of adjuvant topical immunotherapy BCG was described by Herr.
  - i. The procedure used was based on the instillation of citric acid, glucono-delta-lactone, and magnesium carbonate to dissolve kidney stones and involved monitoring renal pressures using a manometer, daily urine cultures, and prophylactic antibiotics.
  - ii. The underlying premise was to prevent high renal pressure and kidney damage, as a kidney stone was causing an obstruction.
  - iii. Although pressure monitoring continues to be mentioned in most reviews, detailed discussions regarding renal pressure in patients with urinary tract cancer were not found.
- (b) *European Association of Urology Guidelines on Upper Urinary Tract Urothelial Cell Carcinoma* states that the antegrade instillation of BCG or mitomycin C in the upper urinary tract by percutaneous nephrostomy via a three-valve system open at 20 cm (after complete tumor eradication) is feasible (Rouprêt et al., 2015). Other studies and research reviews also describe this procedure (Giannarini et al., 2011; Studer et al., 1989). Draganski et al. (2017) did not include interventions to maintain low pressures in the renal pelvis.
- (c) Assemble equipment for administration.
  - i. For administration and monitoring pressure using a manometer, the medication should be mixed in a minibag (e.g., 50 ml) rather than a syringe. The use of microbore tubing decreases drug waste in the IV tubing and ensures the patient will obtain the maximum amount of the medication. The tubing should have a roller clamp and CSTD.
  - ii. The medication, IV tubing, and three-way stopcock should be connected to a manometer and an additional extension tubing. The tubing, stopcock, and manometer should be primed with normal saline prior to attaching to the medication.
  - iii. The manometer can be secured to the IV pole at the level of the patient's kidneys.
  - iv. The medication should hang no more than 20–30 cm above the level of the patient's kidney (Giannarini et al., 2011; Studer et al., 1989).
  - v. Do not use an IV pump.
  - vi. Wear PPE, which includes a gown tested for use with chemotherapy. If unavailable, use a lint-free gown made of a low-permeability fabric, such as polypropylene or other laminate materials, and two pair of gloves tested for use with chemotherapy. Mask and face protection should also be used. Place the patient in a supine position or on their side with the nephrostomy tube side up (Giannarini et al., 2011; Studer et al., 1989).
  - vii. Place a plastic-backed pad under the patient's hips.
  - viii. Cleanse the cap on the nephrostomy tube with an antiseptic per hospital policy. Scrub for 15 seconds. Let dry. If a needleless connector is used for the cap, the IV tubing can be screwed into this. If not, remove the cap and connect it to the IV tubing.
  - ix. Before starting the infusion, check renal pressure using the manometer. To do this, turn the stopcock off in the direction of the medication. Document the number. Do not proceed and notify the provider if the renal pressure exceeds 20 mm Hg (Giannarini et al., 2011; Studer et al., 1989). Check the pressure every 15 minutes and after the end of the infusion.
  - x. Open the stopcock so that the medication flows to the nephrostomy tube.
  - xi. Administer over one to two hours as ordered.
  - xii. Discontinue the infusion if the renal pressure exceeds 20 mm

- Hg or the patient complains of discomfort. Notify the provider.
  - xiii. After the infusion, disconnect the IV tubing. Use personal protective equipment.
  - xiv. Replace the nephrostomy cap. Clean with antiseptic per hospital policy and flush the nephrostomy tube with 10–20 ml normal saline. Replace the nephrostomy tube dressing if needed.
  - xv. Dispose of supplies and personal protective equipment in the appropriate HD container.
- g) Patient education following the procedure (American Urological Association & Society of Urologic Nurses and Associates, 2020)
- (1) Sit when voiding for six hours following the procedure to prevent splashing.
  - (2) Avoid using public toilets. Do not void outside.
  - (3) Increase fluid to dilute the urine.
  - (4) Wash any splashing on skin with soap and water. Wash glans or perineum after voiding.
  - (5) Wear a condom during intercourse until therapy is completed.
  - (6) For BCG, place two cups of bleach in the toilet after each void for six hours following the procedure. Let the bleach sit in the toilet for 15 minutes. Cover the toilet, and flush twice.
  - (7) Common side effects include low-grade fever, urinary frequency and urgency, bladder spasms, burning with urination, and fatigue.
  - (8) Remove clothes if contaminated with urine and wash separately.
- ### 9. Intra-arterial
- a) Intra-arterial chemotherapy delivers high concentrations of medication directly to the tumor with decreased systemic exposure. It has been used for the following procedures:
- (1) Hepatic arterial infusions
    - (a) Liver metastases derive greater than 80% of their blood supply from the hepatic arterial circulation, whereas healthy hepatocytes obtain blood from the portal circulation (Breedis & Young, 1954). Administration of chemotherapy into the hepatic artery allows selective delivery of the drug to cancer cells while sparing healthy cells.
- (b) Floxuridine is rapidly metabolized by the liver by a first-pass effect, leading to higher levels of drug exposure and decreased systemic side effects (Datta et al., 2019).
- (c) Hepatic arterial infusions may be administered using temporary percutaneous catheters, intra-arterial ports, and implantable, programmable pumps.
- i. Transhepatic arterial chemoembolization (TACE) involves the insertion of a temporary arterial catheter into the femoral artery with the tip location in the hepatic artery. It is indicated for some cases of hepatocellular carcinoma and liver metastasis (Young & Savio, 2021).
    - A radiologist injects chemotherapy into the arterial catheter, usually in the interventional radiology suite. The chemotherapy may be mixed with lipiodol (a contrast agent), and an embolization agent or drug-eluting beads are mixed with the chemotherapy. The beads slowly release the chemotherapy. The catheter is discontinued after the procedure, and the patient is monitored for post-procedure complications.
    - Postprocedure care involves assessing circulation in the extremity, bleeding, management of pain and nausea, and postprocedure chemical hepatitis (often delayed) (Yane et al., 2013).
  - ii. Intra-arterial ports used for hepatic artery infusions consist of an implanted port connected to an arterial catheter threaded into the hepatic artery.
  - iii. Implanted programmable pumps are connected to a catheter threaded into the hepatic artery.
- (2) Isolated limb perfusion
- (a) Isolated limb perfusion has been used for melanomas and sarcomas (Broman & Zager, 2019; Neuwirth et al., 2017).

- (b) Depending on the procedure, hyperthermia techniques or tourniquets may be used while administering chemotherapy (Broman & Zager, 2019; Neuwirth et al., 2017).
  - (c) Complications include bleeding, thrombosis, discomfort, and compartment syndrome (Broman & Zager, 2019; Neuwirth et al., 2017).
- (3) Brain tumors
  - (a) Intra-arterial chemotherapy has been used for various brain tumors, including glioblastomas and primary central nervous system lymphomas (Huang et al., 2020; Su et al., 2016). Agents used include carmustine and cisplatin.
  - (b) A temporary arterial catheter is placed in surgery or interventional radiology, and chemotherapy is infused by a physician.
  - (c) Blood–brain barrier and blood–tumor barrier disruption (using medications such as mannitol or bradykinin) may be used to increase the direct entry of medications into the tumor (Huang et al., 2020; Su et al., 2016).
  - (d) Complications from carotid and vertebral infusions reported include severe vascular toxicity and neurotoxicity. Patients with primary glioblastomas or anaplastic astrocytomas receiving intra-arterial cisplatin can experience a significant loss in high-frequency hearing, decreased visual acuity, and irreversible encephalopathy (Huang et al., 2020; Su et al., 2016).
- (4) Retinoblastoma
  - (a) A catheter is introduced through the femoral arterial and advanced to the ostium of the ophthalmic artery (Manjandavida et al., 2019; Rishi et al., 2020). Chemotherapy is then administered in a pulsatile manner over approximately 30 minutes by a physician.
  - (b) Examples of agents used include carboplatin, melphalan, and topotecan (Manjandavida et al., 2019; Rishi et al., 2020).
  - (c) The procedure is performed under general anesthesia.
  - (d) Side effects include local effects on the eye (e.g., edema, hemorrhage, vision changes) and systemic effects (e.g., stroke, ischemia) (Manjandavida et al., 2019; Rishi et al., 2020).
- b) Pretreatment assessment (in addition to the general pretreatment assessment)
  - (1) Prior to placing an arterial catheter, an angiogram or similar dye study is performed to confirm location and arterial blood flow and assess for complications.
  - (2) When temporary percutaneous catheters are used, assess the peripheral circulation of the affected extremity to serve as a baseline (e.g., color, pulse, temperature).
  - (3) Review any laboratory values as indicated for the procedure, such as complete blood count and differential, coagulation studies, liver function tests, and renal function tests.
- c) System safeguards to prevent errors and manage emergencies (see Chapters 1, 12, and 13)
  - (1) Clearly label external lines as intra-arterial and IV to prevent accidental administration of medications via the wrong route.
  - (2) When administering medications and fluids, trace all catheters and lines from the access site into the patient's body.
  - (3) Route intra-arterial tubing and IV tubing to different sides of the bed or chair.
  - (4) Infuse any intra-arterial fluids through tubing without Y-sites so that other medications cannot accidentally be injected or infused (Camp-Sorrell & Matey, 2017).
  - (5) Immediately prior to administration, verify the medication administration route.
  - (6) Use Luer-lock connections on tubing and tape all connections securely (Camp-Sorrell & Matey, 2017).
  - (7) For temporary percutaneous catheters, immobilize the extremity as indicated to prevent accidental catheter dislodgment (Camp-Sorrell & Matey, 2017).
- d) Dosing: The dosing, duration, and frequency are dependent on individual patient factors and the regimens prescribed.
- e) Verification: Verify the location of the catheter tip by reviewing imaging or operative reports (see section D).
- f) Administration
  - (1) Wear PPE, which includes a gown tested for use with chemotherapy. If unavailable, use a lint-free gown made of a low-permeability fabric, such as polypropylene or other laminate materials, and two pair of gloves tested for use with chemotherapy. Mask and face protection should also be used.

- (2) Temporary percutaneous catheters
  - (a) Temporary percutaneous catheters have been used for regional limb perfusions, carotid artery infusions, and hepatic artery infusions (Camp-Sorrell & Matey, 2017).
  - (b) They are often placed in radiology. The catheter may remain in place for minutes, hours, or several days.
  - (c) The most common insertion sites are the brachial and femoral arteries.
  - (d) Depending on the location and duration of infusion, the patient may have activity restrictions and limb immobilization.
  - (e) Place infusions on a pump.
  - (f) Assess vital signs, circulation, and for hematoma during the infusion and for at least two hours after the catheter is discontinued.
- (3) Intra-arterial ports
  - (a) The portal body is placed subcutaneously, and the port catheter is threaded into the designated artery.
  - (b) Ambulatory infusion pumps have been used to deliver medication.
  - (c) Currently, no ports manufactured in the United States are specifically designed for intra-arterial administration of chemotherapy.
  - (d) The port is accessed per the same procedure as an IV port.
  - (e) All tubings and connections must be secured to prevent disconnection and possible hemorrhage.
- (4) Programmable implanted intra-arterial pumps: Hepatic artery infusion pumps are used to administer chemotherapy for colon cancer that has metastasized to the liver (Parks & Routt, 2015).
  - (a) The chemotherapy commonly infused through an intra-arterial pump is 5-fluorodeoxyuridine. The pump is connected to an arterial catheter threaded into the hepatic artery.
  - (b) At the time of this publication, the only implanted pump approved for hepatic artery infusions in the United States is the Intera 3000™ (Intera Oncology, n.d.). The pump is connected to an arterial catheter that is threaded into the hepatic artery. The pump rate is constant and cannot be programmed to a different rate. To change the dose of medication, the concentration is changed.
  - (c) Multiple specialists are needed to care for patients who receive this complex treatment. Care involves surgically implanting the port, proper dosing of drugs, administering drugs using trained and competent staff, and monitoring for toxicities and catheter-related complications (Napier et al., 2021).
    - i. Always verify the type and model of the pump before administering chemotherapy.
    - ii. Pump insertion (Napier et al., 2021)
      - The pump is inserted in surgery or interventional radiology. It is placed in an SC pocket, and the catheter is threaded into the hepatic artery.
      - Pump delivery rates are specific for the brand of pump. Some pumps have a constant rate and cannot be programmed. The concentration is changed to change the dose of medication. However, other pumps have a changeable rate programmed with an external computer.
      - The surgeon will verify the tip of the catheter is appropriately placed; this is usually confirmed with a dye study at the time of placement.
      - Always verify the rate of administration by reviewing the product information. The rate varies with the pump model and individual patient characteristics.
      - Always verify the reservoir volume before administering medication. The volume varies with the model.
      - Pumps generally must be refilled every two weeks; refer to the provider order. A common schedule is two weeks of chemotherapy and

then two weeks of heparinized saline.

- A special straight noncoring needle is used to access the septum in the pump. Refer to specific pump instructions for more information on the procedure.

#### 10. Intrapleural

a) Intrapleural chemotherapy is used to manage malignant pleural effusions using pleurodesis.

(1) Pleurodesis is performed by draining pleural fluid and instilling an irritant (sclerosing agent) through a chest tube. The agent causes inflammation and fibrosis, leading to adhesions between the two pleural membranes. The adhesions prevent pleural fluid from accumulating in the pleural space.

(2) Chemotherapy agents that have been used for pleurodesis include bevacizumab, bleomycin, cisplatin, cytarabine, doxorubicin, etoposide, 5-fluorouracil, and mitomycin C (Heffner, 2020).

b) Physicians and advanced practice providers typically perform pleurodesis. Prior to performing pleurodesis, verify it is within scope of practice by the state board of nursing and institutional policy.

c) Pretreatment assessment (in addition to the general pretreatment assessment)

(1) Assess the volume of pleural fluid in the chest tube drainage system. The daily drainage should be less than 150 ml/24 hours to perform pleurodesis, ensuring that the sclerosis agent has maximum contact with the pleura (Cope, 2018; Heffner, 2020; Hospira, 2021). The literature suggests that successful pleurodesis is partly dependent on complete drainage of the pleural fluid and reestablishment of negative intrapleural pressure prior to the instillation of a sclerosing agent (Cope, 2018).

(2) Perform a baseline respiratory assessment, including rate, depth, and breath sounds.

d) System safeguards to prevent errors and manage emergencies: Intrapleural chemotherapy administration must be performed by an authorized prescriber (see Chapters 1, 12, and 13).

e) Dosing: The sclerosing agent is dissolved in 100–150 ml of normal saline (Heffner, 2020; Hospira, 2021).

f) Verification: Trace all lines to their point of origin (see section D).

#### g) Administration

(1) Premedicate the patient with analgesics if indicated. Some providers instill lidocaine into the chest tube prior to the sclerosing agent (Heffner, 2020).

(2) Wear PPE, which includes a gown tested for use with chemotherapy. If unavailable, use a lint-free gown made of a low-permeability fabric, such as polypropylene or other laminate materials, and two pair of gloves tested for use with chemotherapy. Mask and face protection should also be used.

(3) Use a CSTD on the chemotherapy if compatible with the chest tube system.

(4) Aseptic technique should be maintained throughout the procedure. Any access ports on the tubing should be cleansed with antiseptic per hospital policy.

(5) Chest tube suction should be turned off during the instillation and dwell time. Any stopcocks or clamps should be closed between the site of medication instillation and the chest tube drainage system.

(6) The medication should be administered slowly as per patient tolerance.

(7) Allow the agent to remain for the prescribed dwell time if tolerated. Some references recommend that the patient rotate side to side to distribute the medication, although no evidence supports this practice (Heffner, 2020; Hospira, 2021).

#### h) Postprocedure

(1) After the dwell time is completed or if the patient cannot tolerate the procedure, allow the medication to drain into the chest tube collection system.

(2) Observe during and after the procedure for signs and symptoms of respiratory distress, pneumothorax, infection, and pain.

(3) Dispose of personal protective equipment and supplies in the appropriate HD container.

(4) A chest x-ray may be ordered 24 hours after the procedure. If the chest x-ray indicates no buildup of pleural fluid, the chest tube may be discontinued.

(5) When the chest tube is discontinued or the collection system is changed, do not drain the fluid from the container. Securely wrap the container in an HD bag and dispose of it in the appropriate container.



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## CHAPTER 12

# Safe Handling of Hazardous Drugs

### A. Safe handling and disposal of hazardous drugs (HDs)

1. Many drugs used to treat cancer are hazardous to healthcare workers. HDs require special handling because occupational exposure may cause adverse health effects. These effects occur because of the inherent toxicities of the drugs (American Society of Health-System Pharmacists [ASHP], 2006; National Institute for Occupational Safety and Health [NIOSH], 2004).
2. According to the Occupational Safety and Health Administration (OSHA, 2016), a safe level of occupational exposure to HDs is unknown. Healthcare workers who handle HDs may be at risk for exposure to multiple agents on any given day, and no reliable method for monitoring work-related exposure exists.
3. Therefore, those who work with HDs must adhere to practices designed to minimize occupational exposure.

### B. Definition

1. In 1990, ASHP (then known as the American Society of Hospital Pharmacists) provided the first definition of HDs.
2. ASHP's initial list included four characteristics in determining if a drug is hazardous. Two additional characteristics were later added (NIOSH, 2004).
  - a) Carcinogenicity
  - b) Teratogenicity or developmental toxicity in a fetus
  - c) Reproductive toxicity
  - d) Organ toxicity at low doses
  - e) Genotoxicity
  - f) New drugs similar in structure or toxicity to drugs classified as hazardous using the preceding criteria

### C. Antineoplastic drugs

1. Antineoplastic drugs are also referred to as chemotherapy or cytotoxic drugs used to treat cancer. NIOSH also classifies most antineoplastic drugs as HDs (NIOSH, 2017).

2. Potential adverse health effects of occupational exposure to antineoplastic drugs include increased incidence of cancer in exposed nurses and other healthcare workers.

- a) Published evidence regarding cancer among occupationally exposed nurses and other healthcare workers is limited because of the failure to connect exposure to health outcomes (Blair et al., 2001; Ekpanyaskul & Sangrajrang, 2018; Hansen & Olsen, 1994; Levin et al., 1993; Martin, 2005; Petralia et al., 1999).

- b) In 2019, the National Toxicology Program (NTP) reviewed available studies on cancer. It cited low confidence that occupational exposure to antineoplastic drugs is associated with cancer due to the limited studies of any one cancer site, limited ability to reach level-of-evidence conclusions, and risk-of-bias concerns (NTP, 2019).

- c) The International Agency for Research on Cancer (2022) publishes independent assessments of the carcinogenic risks of chemicals. It has identified 11 antineoplastic drugs and several combination chemotherapy regimens as known human carcinogens. Other antineoplastic agents are classified as probable or possible carcinogens (see Table 12-1).

3. Structural defects in a fetus following occupational HD exposure during pregnancy have been reported (Hemminki et al., 1985; Peelen et al., 1999). No studies of congenital malformations have reported data collected after 2000 (Connor et al., 2014).

4. Adverse reproductive outcomes have occurred in nurses and other healthcare workers exposed to HDs during pregnancy, including miscarriage, infertility/subfertility, preterm births, and learning disabilities in offspring (Connor et al., 2014; Fransman et al., 2007; Lawson et al., 2012; Martin, 2005; Quansah & Jaakkola, 2010).

- a) Most recently, a suggestive association between HD handling and miscarriage was found in a large sample of Nurses' Health Study 3 participants, particularly among nurses who did not

**TABLE 12-1.** Antineoplastic Agents Classified as Carcinogens

| Exposure Risk                             | Antineoplastic Drugs                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|-------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Group 1: Carcinogenic to humans           | <ul style="list-style-type: none"> <li>• Arsenic trioxide<sup>a</sup></li> <li>• Azathioprine</li> <li>• Busulfan</li> <li>• Chlorambucil</li> <li>• Cyclophosphamide</li> <li>• Etoposide</li> <li>• Etoposide in combination with cisplatin and bleomycin</li> <li>• Melphalan</li> <li>• MOPP (mechlorethamine hydrochloride, vincristine, procarbazine, and prednisone)</li> <li>• Semustine</li> <li>• Tamoxifen</li> <li>• Thiotepa</li> <li>• Treosulfan</li> <li>• Other combined chemotherapy including alkylating agents</li> </ul> |
| Group 2A: Probably carcinogenic to humans | <ul style="list-style-type: none"> <li>• Azacitidine</li> <li>• Carmustine<sup>a</sup></li> <li>• Cisplatin</li> <li>• Doxorubicin<sup>a</sup></li> <li>• Nitrogen mustard</li> <li>• Procarbazine hydrochloride</li> <li>• Teniposide</li> </ul>                                                                                                                                                                                                                                                                                             |
| Group 2B: Possibly carcinogenic to humans | <ul style="list-style-type: none"> <li>• Amsacrine</li> <li>• Bleomycin</li> <li>• Dacarbazine</li> <li>• Mitomycin C</li> <li>• Mitoxantrone</li> <li>• Streptozocin</li> </ul>                                                                                                                                                                                                                                                                                                                                                              |

<sup>a</sup>Although not on International Agency for Research on Cancer list, package insert is consistent with that risk category.

Note. Based on information from International Agency for Research on Cancer, 2022.

consistently use personal protective equipment (PPE) and engineering controls (Nassan et al., 2021). Recent evidence suggests that increased adherence to using PPE and engineering controls has improved the time to conception (Nassan et al., 2019).

- b) NTP also reviewed reproductive toxicities and miscarriage. Although the program reported very low confidence that occupational exposure to antineoplastic drugs during pregnancy is associated with reproductive and developmental toxicity, it cited moderate confidence that occupational exposure to antineoplastic drugs during pregnancy is associated with miscarriage (NTP, 2019).

5. Cytogenetic effects have occurred in healthcare workers following exposure to HDs, including

chromosomal damage, chromosomal aberrations, increased frequency of micronuclei, oxidative stress and mitochondrial damage, and apoptosis (Bouraoui et al., 2011; Buschini et al., 2013; Eghbal et al., 2018; El-Ebiary et al., 2013; Ladeira et al., 2014; Liao et al., 2017; Mahmoodi et al., 2017; McDiarmid et al., 2010, 2014; Moretti et al., 2015; Ramazani et al., 2019; Roussel et al., 2019; Santovito et al., 2014; Villarini et al., 2011; Villarini et al., 2016).

6. Acute symptoms have been documented in exposed healthcare workers, such as hair loss, abdominal pain, fatigue, nausea, nasal irritation or sores, contact dermatitis, allergic reactions, skin injury, eye injury, and changes in blood work (Baykal et al., 2009; Caciari et al., 2012; Constantinidis et al., 2011; Meyer & Skov, 2010; Simons & Toland, 2017).

a) NTP cited very low confidence that occupational exposure to antineoplastic drugs is associated with acute effects because of the degree of heterogeneity in the outcomes and risk of bias concerns (NTP, 2019).

b) A recent study demonstrated that spills are common occurrences, and PPE use is suboptimal during spill cleanup (Friesen et al., 2020). Exploration of the acute symptoms experienced by those involved in spills, which pose a greater risk for acute exposure, is needed.

#### D. NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings, 2016

1. NIOSH provides a list of HDs and periodic updates at [www.cdc.gov/niosh/topics/hazdrug](http://www.cdc.gov/niosh/topics/hazdrug). At the time of this writing, the 2016 list is still in use. A 2020 revision is in draft form and can be viewed at [www.federalregister.gov](http://www.federalregister.gov).
2. The list is divided into three groups.
  - a) Group 1 includes antineoplastic drugs that meet one or more of the criteria for HDs. This group includes chemotherapy agents, targeted agents, and other biologic drugs used in cancer treatment.
  - b) Group 2 involves nonantineoplastic drugs that meet one or more of the criteria for HDs. This group includes drugs from several categories, including immunosuppressant agents, antivirals, anticonvulsants, estrogens, progestins, and androgens.
  - c) Group 3 includes nonantineoplastic drugs with primarily reproductive effects. These are drugs from different classifications that are harmful to men and women actively trying to conceive and women who are pregnant or breastfeeding.

#### E. NIOSH List of Hazardous Drugs in Healthcare Settings, 2020

1. The proposed 2020 NIOSH revisions retitled and reorganized the drug listing. Antineoplastic drugs are no longer all cytotoxic, genotoxic, and highly hazardous chemicals. NIOSH determined that grouping all antineoplastic drugs together in one table was no longer the most useful or informative for users and regrouped the tables by hazard.
2. This pending list is divided into two tables.
  - a) Table 1 includes drugs that contain a manufacturer's special handling information in the package insert or meet the NIOSH definition of an HD and are classified by NTP as "known to be a human carcinogen" or classified by the International Agency for Research on Cancer as "carcinogenic" or "probably carcinogenic" (Hazardous Drugs, 2020).
  - b) Table 2 includes drugs that meet the NIOSH definition of an HD but do not have a manufacturer's special handling information and are not classified by NTP as "known to be a human carcinogen" or classified by the International Agency for Research on Cancer as "carcinogenic" or "probably carcinogenic" (Hazardous Drugs, 2020).

#### F. Immunotherapy

1. Immunotherapy uses the patient's immune system to manage or eradicate diverse cancer types (Farkona et al., 2016). Six categories of immunotherapy approaches have been described in this book: checkpoint inhibitors, chimeric antigen receptor T cells, cytokines, immunomodulators, monoclonal antibodies (mAbs) (e.g., radioimmunotherapy), and oncolytic viral therapies.
2. Harm from occupational exposure to mAbs was believed to be minimal because of the low likelihood of internalizing the large molecules through the usual exposure routes (Halsen & Krämer, 2011); however, no direct evidence supports a particular molecular weight above which a drug cannot achieve a detectable level following repeated occupational exposure (de Lemos et al., 2018).
  - a) NIOSH does not list all mAbs as hazardous; instead, each is compared to the criteria for HDs.
  - b) Pertuzumab is hazardous because of embryo-fetal death (NIOSH, 2016).
  - c) Conjugated mAbs are hazardous because of the attached radioactive isotopes (e.g., tositumomab) or toxins (e.g., ado-trastuzumab, brentuximab vedotin, gemtuzumab ozogamicin, loncastuximab tesirine-lpyl, sacituzumab govitecan, belantamab mafodotin, polatuzumab vedotin, enfortumab vedotin, inotuzumab ozogamicin, trastuzumab deruxtecan) (NIOSH, 2016). Antibody-drug conjugates are becoming increasingly popular, with many approved in the past five years.
    - d) For mAbs conjugated with antineoplastic drugs or radioactive particles, see Chapter 10. Use safe handling precautions (e.g., PPE, closed-system drug-transfer devices [CSTDs], containment primary engineering control [C-PEC]) for immunotherapy drugs conjugated with antineoplastic drugs or radioactive particles, as these drugs are considered hazardous (NIOSH, 2016).
    - e) Based on the mechanism of action, some mAbs may cause developmental toxicity, including alemtuzumab, bevacizumab, cetuximab, panitumumab, rituximab, and trastuzumab (Halsen & Krämer, 2011); however, NIOSH (2016) does not classify these agents as HDs.
    - f) A nuclear pharmacist prepares radiolabeled mAbs for infusion. Federal and state laws require that radiation safety warning signs be placed to designate areas where radioisotopes are stored or used (McQuestion et al., 2021).
    - g) NIOSH guidelines and the package insert should be followed to determine the required PPE. Some institutions may require all PPE during the administration of mAbs because they are often given in combination or conjugated with other HDs. This makes PPE requirements simple for staff.
3. Several targeted agents meet one or more of the criteria in the NIOSH definition of HDs and should be handled as hazardous (e.g., handled with PPE and not crushed). Refer to the most recent NIOSH publication for a list of these agents (NIOSH, 2016).
4. Limited data regarding the effects of occupational exposure on these agents are available. It is unclear whether the criteria in the definition of HDs are adequate for protein-based or bioengineered drugs (Halsen & Krämer, 2011; NIOSH, 2016).
5. Novel viral-based therapies require contact isolation and PPE for infection prevention because patients may shed the viruses (Martin, 2017).
6. Most nonconjugated biologic agents do not affect DNA and thus do not cause genetic changes.
7. Antiangiogenic agents (e.g., lenalidomide, thalidomide) pose a risk to fetuses (Celgene, 2019, 2021).

#### G. Routes of occupational exposure include absorption through the skin or mucous membranes following direct drug contact or contact with surfaces or objects that are contaminated with HDs.

1. Many studies reported measurable levels of antineoplastic drugs in the urine of healthcare workers, most likely from dermal absorption (Canal-Raffin et al., 2016; Connor et al., 2010; Friese et al., 2014; Hama et al., 2012; Hon et al., 2015; Izzo et al., 2018; Miyake et al., 2013; Ndaw et al., 2010; Pieri et al., 2010; Ramphal et al., 2014, 2015; Sabatini et al., 2012; Sottani et al., 2010; Sugiura et al., 2011; Yoshida et al., 2011; Zhang et



al., 2016). Some evidence suggests that improvements in safe handling practices have led to reduced exposure for workers (Koller et al., 2018; Poupeau et al., 2017).

2. Multiple studies have documented contamination of surfaces with HDs in drug preparation, administration, and patient care areas (Berruyer et al., 2015; Bussi res et al., 2012; Chu et al., 2012; Connor et al., 2010; Guichard et al., 2019; Kopp et al., 2013; Ladeira et al., 2014; Maeda et al., 2010; Miyake et al., 2013; Moretti et al., 2015; Ramphal et al., 2014; Salch et al., 2019; Sottani et al., 2012; Sugiura et al., 2011; Villarini et al., 2011; Walton et al., 2020; Yoshida et al., 2011). These findings indicate that anyone in these areas not wearing PPE when touching surfaces contaminated with HD residue is at risk for exposure.
3. Several researchers have reported drug contamination on the outside of drug vials when delivered by the manufacturers (Connor et al., 2005; Fleury-Souverain et al., 2014; Hama et al., 2012; Kopp et al., 2013; Schierl et al., 2010). Cyclophosphamide, 5-fluorouracil, ifosfamide, and platinum have been detected on vial exteriors using various sampling techniques. These findings indicate that health-care workers may be exposed if they do not wear PPE while handling unopened drug vial.
4. Other routes of exposure
  - a) Injection from needlesticks or contaminated sharps (ASHP, 2006; NIOSH, 2004)
  - b) Inhalation of drug aerosols, dust, or droplets (Fent et al., 2014; Kiffmeyer et al., 2002)
  - c) Ingestion of contaminated foods, beverages, tobacco products, or other hand-to-mouth behaviors (NIOSH, 2004)

#### H. Hierarchy of hazard controls aimed at reducing worker exposure (NIOSH, 2015)

1. Elimination of the hazard: The highest level of protection from hazardous exposure is to eliminate the hazard, but this is not feasible with drug therapy.
2. Substitution of the hazard: The second-highest level of protection from hazardous exposure is to replace the hazard by substituting a less toxic substance, but this is also not feasible with drug therapy.
3. Engineering controls: The third highest level of protection is to use engineering controls—machines or equipment—that isolate or contain the hazard to reduce worker exposure. Examples include CSTDs and biosafety cabinets.
4. Administrative controls: The fourth level of protection includes safe handling policies, procedures, work practices, and education and training of those responsible for HD handling.
5. PPE: Despite being the lowest on the NIOSH hierarchy and placing the primary responsibility on the worker, PPE is an important aspect of multilevel

efforts for the protection of healthcare workers and consists of garments that provide barriers to protect workers from HDs.

#### I. Guidelines for PPE

##### 1. Apparel

a) Gloves: Wear two pairs of disposable gloves that are powder free and have been tested for use with HDs (U.S. Food and Drug Administration [FDA], 2020).

- (1) FDA requires permeation testing for gloves to be labeled as appropriate for use with HDs. Gloves are not tested for all known HDs because of the cost and lack of assays for many drugs; however, for gloves to be labeled for use with HDs, they must be tested with seven drugs from different classifications: carmustine, cyclophosphamide, doxorubicin, etoposide, 5-fluorouracil, paclitaxel, and thiopeta (ASTM International, 2019; Polovich & Olsen, 2018).
- (2) Gloves that prevent HD permeation for a minimum of 30 minutes should be worn.
- (3) Test results are printed on the glove box or are available from the manufacturer.
- (4) Several types of materials are used to make gloves used for HD handling (e.g., nitrile, polyurethane) (Polovich & Olsen, 2018).
- (5) Tested latex gloves provide protection but should be used with caution because of the potential for latex sensitivity.
- (6) Inspect gloves for physical defects before use.
- (7) Remove and discard gloves immediately after use; if a tear, puncture, or known drug contact occurs; or after 30 minutes of wear (ASHP, 2006; NIOSH, 2004; U.S. Pharmacopeial Convention [USP], 2019).
- (8) Wearing double gloves, with one pair under and one pair over the gown cuff or elastic band, and carefully removing them reduces the opportunity for exposure (NIOSH, 2008).
- (9) When doffing PPE, remove outer gloves, gown, shoe covers (if in use), inner gloves; wash hands with soap and water; don clean gloves to remove mask and face shield (if in use); doff gloves; and rewash hands.

b) Gowns: Wear a disposable, lint-free gown made of a low-permeability fabric, such as polyethylene-coated polypropylene or other laminate materials (Connor, 2006; Polovich & Olsen, 2018; USP, 2019).

- (1) The gown should have a solid front, long sleeves, tight cuffs, and back closure.

- (2) Discard the gown when it is knowingly contaminated, before leaving HD handling areas, and when finished with HD handling.
  - (3) Gowns are meant for single use.
  - (4) Used gowns should not be hung up or reapplied after removal. Single-use gowns minimize the transfer of drug contamination to the environment and worker clothing (NIOSH, 2008).
  - (5) All healthcare workers should wear PPE, which includes a gown tested for use with chemotherapy, when cleaning a spill or if there is a risk of spilling or splashing. If unavailable, use a lint-free gown made of a low-permeability fabric, such as polypropylene or other laminate materials, and two pair of gloves tested for use with chemotherapy. Mask and face protection should also be used.
  - c) Respirators: Wear a NIOSH-approved filtering facepiece respirator, such as a fit-tested N95, or a powered air-purifying respirator when inhalation exposure is possible (NIOSH, 2021).
    - (1) Examples include administering an aerosolized HD or cleaning an HD spill.
    - (2) If gases or vapors are present, wear a chemical cartridge-type respirator (USP, 2019).
    - (3) Consult the drug-specific safety data sheet (SDS) for the type of respirator appropriate for the situation. Surgical masks do not provide respiratory protection from HD aerosols.
  - d) Eye and face protection: Wear goggles and a face shield or a combination of goggles, mask, and face shield that provides splash protection whenever HD splashing is possible.
    - (1) Eye and face protection are necessary when administering HDs in an operating room, working at or above eye level, or cleaning up a spill (USP, 2019).
    - (2) When eye and face protection are worn, remove them last, after other PPE is removed and hands are washed with soap and water. Don clean gloves to remove eye and face protection and rewash hands with soap and water once the eye and face protection and gloves have been removed. This prevents the possible transfer of HD to the face. If administering HDs in an airborne isolation room, wash hands with soap and water after removing all PPE and then don clean gloves to remove face and eye protection (which may be contaminated with microorganisms).
  2. Situations requiring PPE: Wear PPE whenever HDs might be released into the environment. NIOSH recommends that gowns and gloves be worn for all HD handling activities and that eye, face, and respiratory protection be used when splashing or inhalation exposure is possible. The only exception is for administering an intact tablet or capsule provided in a unit-dose package, in which case a single pair of HD-tested gloves is sufficient (NIOSH, 2016). The following situations require PPE (NIOSH, 2004):
    - a) Handling HD vials, ampules, or packaging materials
    - b) Introducing or withdrawing needles or dispensing pins from HD vials
    - c) Transferring drugs from HD vials to other containers using needles or dispensing pins and syringes
    - d) Opening ampules of HDs
    - e) Administering HDs by any route
    - f) Handling HD leakage from tubing, syringe, and connection sites
    - g) Discontinuing infusions of HDs
    - h) Disposing of HDs and items contaminated by HDs
    - i) Handling the body fluids of a patient who has received HDs recently
    - j) Cleaning HD spills
    - k) Touching any surface potentially contaminated with HD residue
- J. Storage and labeling
1. Clinical areas
    - a) Store HD drug containers in a designated location that limits exposure to healthcare workers and provides appropriate storage conditions (e.g., temperature, light).
    - b) Use a distinct label on all HD containers to indicate the hazardous nature of the contents (OSHA, 2016).
    - c) Have access to instructions (e.g., SDSs) regarding what to do for accidental HD exposure.
    - d) Check HD containers before taking them from the storage area to ensure that the packaging is intact and to detect any leakage or breakage.
  2. Patient instructions for HD safety in the home (Polovich & Olsen, 2018; see Figure 12-1)
    - a) Keep HDs out of reach of children and pets.
    - b) Store HDs in containers that protect them from puncture or breakage.
    - c) Label HD containers to indicate the hazardous nature of their contents.
    - d) Provide instructions listing the procedure for handling a damaged HD container.
    - e) Store HDs in an area free of moisture and temperature extremes. Some HDs may require refrigeration.

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**FIGURE 12-1. Safe Management of Hazardous Drugs in the Home**

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You are getting medicine used to treat cancer. You must be careful to make sure other people do not accidentally touch the drugs or your body waste (urine, bowel movements, vomit) for a time after treatment. This form teaches you and your family how to protect others from the drugs and how to handle your body waste in your home.

**Hazardous Drugs**

Hazardous drugs are strong chemicals. Only patients who need treatment should take or touch the drugs. Items that touch the medicines (syringes, needles) are contaminated with drugs. Regardless of how you take the medicines, they remain in your body for many hours and sometimes days after your treatment. Your body will get rid of the drugs in your urine or bowel movements. Traces of the drugs also may be present in vomit, sweat, blood, semen, vaginal fluid, and saliva.

**Disposal of Hazardous Drugs**

Dispose of items contaminated with hazardous drugs separately from other trash. If required, the company supplying your medicines and equipment will give you a hard plastic container labeled with "Hazardous Drug Waste" or a similar warning. Place equipment and gloves that have touched these drugs into this container after use. If the waste is too large to fit in the plastic container, place it in a separate plastic bag and seal it tightly with rubber bands. Place sharp objects in the hard plastic container. The company will tell you who will pick up the disposal container.

*Body Waste*

You may use the toilet (septic tank or sewer) as usual. Flush with the lid closed for 48 hours after receiving these drugs. No research supports the effectiveness of double flushing; however, it may be helpful with low-volume flush toilets. Wash your hands well with soap and water afterward, and wash your skin if urine or bowel movement gets on it. Pregnant women, children, and pets should avoid touching the drugs or contaminated waste.

*Laundry*

Wash your clothing or linens normally, unless they become soiled with the drugs or body fluids, such as urine, bowel movement, or vomit. If that happens, put on disposable gloves and handle the laundry carefully to avoid getting the drugs on your skin. If you do not have a washer, place soiled items in a plastic bag until they can be washed. Wash separately from other laundry.

*Skin Care*

Hazardous drugs spilled on the skin may be irritating. If this happens, thoroughly wash the area with soap and water, then dry. Call your doctor if redness lasts for more than one hour or if a rash occurs. To prevent hazardous drugs from being absorbed through the skin, wear gloves when working with the drugs, drug-soiled equipment, or waste.

*Eye Care*

If any hazardous drug splashes into your eyes, flush them with water for 10–15 minutes and notify your doctor.

**Questions and Answers**

*Is it safe for family members to have contact with me during my treatment?*

Yes. Eating together, enjoying favorite activities, hugging, and kissing are all safe.

*Is it safe for my family to use the same toilet as I do?*

Family members should use separate toilets from the patient for 48 hours after hazardous drug administration to eliminate the risk of contact with contaminated body waste. In households with only one bathroom, patients can keep sanitizing wipes near the toilet to clean the seat and rim after use. The wiping action physically removes hazardous drug residue from surfaces. Following toileting and cleaning, patients should wash their hands with soap and water before touching other surfaces or items. At the end of 48 hours, the toilet and bathroom floor should be washed (Polovich & Olsen, 2018).

*What should I do if I do not have control of my bladder or bowels?*

Use a disposable, plastic-backed pad, diaper, or sheet to soak up urine or a bowel movement. Change immediately when soiled, and wash skin with soap and water. If you have an ostomy, your caregiver should wear gloves when emptying or changing the bags. Discard disposable ostomy supplies in the hazardous drug waste container.

*What if I use a bedpan, urinal, or commode?*

Your caregiver should wear gloves when emptying body wastes. Reusable items contaminated with body fluids during and for at least 48 hours after therapy should be handled with gloves and washed with soap and water.

*What if I vomit?*

Your caregiver should wear gloves when emptying the basin. The container should be washed with soap and water.

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(Continued on next page)

**FIGURE 12-1.** Safe Management of Hazardous Drugs in the Home (*Continued*)*Is it safe to be sexually active during my treatment?*

Ask your doctor or your nurse this question. Traces of hazardous drugs may be present in vaginal fluid and semen for up to 48 hours after treatment. Special precautions may be necessary.

*How should I store hazardous drugs at home?*

You should store hazardous drugs and equipment in a safe place, out of reach of children and pets. Do not store hazardous drugs in the bathroom, as high humidity may damage the drugs. Check medicine labels to see if your drugs should be kept in the refrigerator or away from light. Be sure all medicines have complete labels.

*Is it safe to dispose of hazardous drugs in the trash?*

No. Hazardous drug waste is dangerous and requires separate handling. If you are receiving IV drugs at home, you should have received a special waste container for the drugs and equipment. This includes used syringes, needles, tubing, bags, cassettes, and vials. This container should be hard plastic and labeled with "Hazardous Drug Waste" or a similar warning. Follow disposal instructions from your healthcare team.

*Can I travel with my hazardous drugs?*

Yes. Usually, traveling is no problem. Some hazardous drugs require special storage (refrigeration), so you may need to make special arrangements. Check with your nurse, doctor, or medicine supplier for further instructions. Regardless of your means of travel (airplane, car), always seal your drugs in a plastic bag.

*What should I do if I spill some hazardous drugs?*

You will have a spill kit if you receive IV drugs at home. In the event of a drug spill, open the spill kit and put on two pairs of gloves, the mask, gown, and goggles before touching anything. Move others away from the spill. Absorb the spill with the disposable sponge or towels, and put them directly in the bag provided. Clean the area with dishwashing soap or detergent and water. If the spill occurs on sheets or clothing, handle them with gloves and wash them separately from other laundry. Wash clothing or bed linen soiled with body wastes in the same manner. Remove the face shield, mask, gown, and then the gloves. Place them in the plastic bag and close it. Place the first plastic bag into a second plastic bag and close it. Wash your hands with soap and water. Call the home health nurse, clinic, or doctor's office promptly to report the spill. They will let you know about plans to replace the spilled drug to complete treatment. They will also arrange to pick up the waste material or tell you where to bring it for proper disposal.

- f) Provide HD spill kits and instructions for use.
- g) Give verbal and printed or electronic instructions about handling and storing HDs, disposing of HD waste, and what to do with unused drugs.

## K. Safe handling precautions during compounding

1. USP (2019) General Chapter 800 (<800>) describes standards for the preparation of HDs. The environment in which sterile HD preparation takes place must meet all requirements for ventilation, including air exchanges per hour, particle counts, and negative pressure. See USP (2019) for the complete standards. Additionally, nonsterile drugs must be prepared following standards in Pharmaceutical Compounding—Nonsterile Preparations <795> and sterile compounding must follow standards in <797>.
2. Engineering controls
  - a) Engineering controls for compounding are divided into three categories—primary, secondary, and supplemental.
  - b) Sterile and nonsterile HDs should be prepared in a C-PEC, a ventilated device that minimizes worker and environmental HD exposure when directly handling HDs (USP, 2019).

- c) The containment secondary engineering control is the room in which the C-PEC is placed.
- d) Supplemental engineering controls, such as CSTDs, are adjunct controls to offer additional levels of protection (USP, 2019).
- e) According to NIOSH (2004), a CSTD is "a drug transfer device that mechanically prohibits the transfer of environmental contaminants into the system and the escape of hazardous drug or vapor concentrations outside the system" (p. 44). CSTDs are supplementary engineering controls and do not eliminate the need for a C-PEC or PPE (NIOSH, 2004; USP, 2019).
- f) Requirements for C-PECs
  - (1) The C-PEC must be located in a containment secondary engineering control, an area physically separate from other preparation areas and at negative pressure relative to an adjacent ante area (USP, 2019).
  - (2) It must be externally vented (preferred) or have redundant HEPA filters in series vented to the outside (USP, 2019).
  - (3) Examples include CVE (containment ventilated enclosure), class I–II biosafety cabinet, and CACI (compounding aseptic containment isolator).

- (4) The C-PEC must be used by individuals trained to employ techniques that reduce contamination.
  - (5) It must be cleaned, decontaminated, and disinfected at the end of drug preparation or immediately if a spill occurs (USP, 2019).
  - (6) The C-PEC must be serviced according to the manufacturer's recommendations.
  - (7) It must be recertified after relocation, repair, filter replacement, or every six months (Gilpin, 2018; OSHA, 2016).
  - (8) When nonsterile HDs are being prepared, such as oral drugs that require compounding or crushing, a separate C-PEC should be used (NIOSH, 2016; USP, 2019). The same C-PEC designated for sterile preparations may be occasionally used, but it must be decontaminated, cleaned, and disinfected afterward (USP, 2019). For entities that compound nonsterile and sterile HDs, the respective C-PECs must be placed in separate rooms unless those used for nonsterile compounding are sufficiently effective that the room can continuously maintain ISO7 classification throughout the nonsterile compounding activity (USP, 2019).
  - (9) A plastic-backed preparation mat should be placed on the work surface of the C-PEC (USP, 2019). The mat should be changed immediately if a spill occurs and regularly during use. It should be discarded at the end of the daily compounding activity. Disposable or clean equipment for compounding (e.g., spatulas) must be dedicated for use with HDs.
  - (10) Limit the number of items placed in the C-PEC to avoid interfering with airflow (ASHP, 2006).
  - (11) Use tubing and syringes with Luer-lock fittings. A CSTD is recommended (USP, 2019).
  - (12) Avoid filling syringes more than three-fourths full (ASHP, 2006). An overfilled syringe may separate from the plunger end. Apply a tightly fitted dead-end Luer cap or a CSTD to the end of the syringe if the dosage form allows. Syringes should not be dispensed with needles attached.
  - (13) In the pharmacy, use a CSTD to minimize leakage and exposure (Sessink et al., 2011, 2013; Siderov et al., 2010; Yoshida et al., 2013).
  - (14) Glass IV bottles should not be used for HDs because of the need for venting and the potential for breakage, which can result in exposure (Polovich & Olsen, 2018).
  - (15) Other activities that should not be performed outside of a C-PEC
    - (a) Expelling air from an HD-filled syringe
    - (b) Spiking IV bags containing HDs with IV tubing, unless a CSTD adapter is used to allow for a dry spike
    - (c) Priming IV tubing with HDs
    - (d) Crushing group 1 HD tablets
  - (16) Place a label on each HD container that says "hazardous drug" or a similar distinct warning.
  - (17) Wipe the outside of the HD container (e.g., syringe, IV bag) with a moistened wipe before placing it in a transparent, sealable bag and then inside an additional bag for transport. Wiping the final preparation will physically remove surface contamination (ASHP, 2006). Discard the wipe as contaminated waste. Avoid transferring HD contaminants to the outside of the transport bag.
  - (18) Dispose of all material that has come into contact with an HD in a waste container designated for hazardous waste.
- g) Requirements for containment secondary engineering control
- (1) Be externally vented
  - (2) Be physically separated (in a different room from other preparation areas)
  - (3) Have an appropriate air exchange
  - (4) Have a negative pressure between 0.01–0.03 inches of water column relative to all adjacent areas (USP, 2019)
- h) Requirements for CSTDs
- (1) CSTDs are a common containment supplemental engineering control, providing additional protection during compounding or administration.
  - (2) Some CSTDs have been shown to limit aerosols during compounding and administration. However, no universal performance standard exists, and CSTDs should be selected based on independent, peer-reviewed studies demonstrating containment reduction.
  - (3) CSTDs cannot substitute for a C-PEC and must be used when administering antineoplastic drugs when the dosage form allows.



- (4) If a CSTD is physically or chemically incompatible with a specific HD, use an alternate CSTD that is compatible (USP, 2019).

i) Requirements for PPE

- (1) Wash hands before donning PPE.
- (2) Wear PPE tested for use with HDs.
- (3) When doffing PPE, remove outer gloves, gown, shoe covers (if used), and inner gloves; wash hands with soap and water; don clean gloves; and remove mask and face shield (if used). Remove gloves and rewash hands.
- (4) For a spill in which a powered air-purifying respirator (PAPR) or chemical cartridge mask is used, a clean pair of gloves should be worn to remove the PAPR/cartridge mask, and it should be placed on a plastic-backed pad. Gloves should then be removed and hands washed. A final pair of gloves would be needed to clean the equipment per the manufacturer's guidelines. After, the gloves should be removed and hands washed again.

L. Transporting HDs (OSHA, 2016)

1. Transport syringes containing HDs in a sealed container with the Luer-lock end of the syringe capped. Do not transport syringes with attached needles.
2. Select a transport receptacle that can contain HD spillage if dropped (e.g., a leakproof, zipper-lock bag), and add impervious packing material as necessary to avoid damage during transport. Double bagging is considered a best practice to minimize the transfer of HD on surfaces during delivery to the administration area.
3. Label the outermost HD receptacle with a distinct label to indicate hazardous contents.
4. Do not transport parenteral antineoplastic drugs or liquid HDs in a pneumatic tube (USP, 2019).
5. Ensure that whoever transports HDs has access to a spill kit and is trained in HD spill cleanup.
6. Personnel who transport HDs must document their training according to OSHA standards and other applicable laws and regulations (USP, 2019).

M. Safe handling precautions during administration (ASHP, 2006; OSHA, 2016; Polovich & Olsen, 2018; USP, 2019; see Appendix G)

1. Don PPE tested for use with HDs before reaching into the delivery bag to remove the drug container. Do not lay the HD container on a surface unless there is a disposable, plastic-backed pad covering the surface.

2. Inspect the drug delivery bag and its contents for leakage prior to handling.
3. Work below eye level.
4. Ensure that a spill kit and HD waste container are available.
5. Wear a mask with face protection if there is a potential for HD splashing.
6. Use a CSTD when the dosage form allows.
7. When a CSTD cannot be used, place a disposable, absorbent, plastic-backed pad on the work area to absorb any drug that may spill.
8. Use needles, syringes, and tubing with Luer-lock connectors.
9. Do not use glass bottles for HDs.
10. When administering HDs as a secondary infusion, it is recommended that back priming using a non-HD solution be used. With consistent use of CSTDs at all access points (e.g., bag spike adapters, Luer lock IV site connectors, IV tubing sets) and appropriate PPE, priming with non-HD solution via backflow/back prime method can assist with maintaining a closed system to prevent exposure. After HD administration, the back prime method can be repeated to flush the drug to ensure full medication delivery (Institute for Safe Medication Practices [ISMP], 2021). Some CSTDs only allow forward or one-way flow, which may limit the ability to back prime. If back priming is not an option, a safe strategy should be used to flush the tubing after administration to ensure the patient receives all the antineoplastic (ISMP, 2021).
11. When administering HDs as a primary infusion, the tubing can be primed with a non-HD solution. The primary tubing can also be primed with a bag of non-HD solution by the nurse, and then the tubing can be spiked into the CSTD infusion adapter spike at the point of administration. Never spike directly into an HD bag without a CSTD infusion adapter spike.
12. For drugs with a high risk of reaction (e.g., rituximab, paclitaxel), it is preferred to prime administration tubing with the drug to be more aware of when it is reaching the patient and better monitor for acute hypersensitivity reaction (see Chapter 11). In these scenarios, it is required for the pharmacy to prime the tubing with the HD drug solution within the C-PEC and deliver this with a CSTD attached to the end of the tubing. It should be clearly labeled that the line is primed with the drug to notify the receiving nurse of this setup. This procedure may also be followed for investigational drugs per sponsor requirements.
13. If using secondary tubing to administer sequential HDs, use a CSTD at the port above the pump so that the tubing can be safely disconnected and discarded with each subsequent dose. Never unspike or unhook a secondary tubing that contains an HD without a CSTD.

14. If using primary tubing to administer sequential HDs, use a CSTD at the closest port to the patient side so that tubing can be safely disconnected and discarded with each subsequent dose.
15. More research is needed on the safety of the circle priming practice. Ideally, the pharmacy should prime the tubing and apply a CSTD to the end of the tubing. If circle priming is a practice approved by individual facilities, policies must ensure strict monitoring of aseptic techniques to prevent microbial contamination and safe handling practices to control for potential exposure. Priming of tubing with HDs even partially should never be performed outside of the C-PEC.
16. After IV drug administration, remove the IV container with the tubing attached (NIOSH, 2004; Polovich & Olsen, 2018). Do not remove the spike from IV containers to reuse tubing.
17. Remove outer gloves before touching equipment.
18. Discard all HD-contaminated material and PPE in a designated hazardous waste container.
19. Wash hands with soap and water (not alcohol-based hand gels) because friction and rinsing are needed to remove HDs.
20. When doffing PPE, remove outer gloves, gown, shoe covers (if used), and inner gloves; wash hands with soap and water; don clean gloves; and remove mask and face shield (if used). Remove gloves and rewash hands.
21. In the event a PAPR or chemical cartridge mask is used, a clean pair of gloves should be worn to remove the PAPR/cartridge mask, and it should be placed on a plastic-backed pad. Gloves should then be removed and hands washed. A final pair of gloves would be needed to clean the equipment per the manufacturer's guidelines. After, the gloves should be removed and hands washed again.
22. Use detergent and water or cleansing wipes to wipe surfaces that come into contact with HDs (Polovich & Olsen, 2018).

#### N. Special precautions for radiopharmaceuticals

1. Special precautions are necessary to protect healthcare workers from exposure while caring for patients receiving radiopharmaceuticals. Radiation protection standards and regulations are determined by the U.S. Nuclear Regulatory Commission, FDA (radiopharmaceuticals), and state radiation regulatory agencies (U.S. Environmental Protection Agency, 2022). Although infusion nurses are not directly administering these drugs, patient body fluids, especially urine, serve as a source of radiation exposure.
2. Occupational radiation exposure should be kept as low as reasonably achievable. Three factors help provide protection (McQuestion et al., 2021).

- a) Time: Limit the time spent near the radioactive source. Radiation exposure is directly proportional to the time spent near the source. After a patient receives radiopharmaceuticals, the patient is considered the radioactive source. The patient's body can absorb or shield many of these particle types, limiting exposure to bystanders and healthcare workers.
- b) Distance: Maximize the space between personnel and the radioactive source. Radiation exposure decreases as the distance from the radioactive source increases.
- c) Shielding: Add a protective barrier between the radioactive source and personnel. The type of shielding used depends on the type of radiation.

3. Radiation monitoring devices are used to measure occupational exposure. An electronic personal dosimeter is the most widely used monitoring device. Healthcare workers who have the potential to receive significantly more than 10% of the annual effective dose limit during their duties (per the judgment of the radiation safety officer) and those who enter radiation areas should have an electronic personal dosimeter. The dosimeter should only be worn within the work environment, be changed according to institutional guidelines, and not be shared with anyone else. Ring dosimeters and pocket ion chamber dosimeters also exist. Monitoring the environment is also recommended (McQuestion et al., 2021).

#### O. Handling body fluids

1. After HDs
  - a) In general, safe handling precautions are recommended when handling a patient's body fluids for at least 48 hours after drug administration; however, some HDs may be present in excreta longer. If information about longer excretion time is known, use precautions for the entirety that HDs are likely to be present. Patients receiving oral HDs are expected to have HD residue in their excreta throughout therapy and at least 48 hours after the final dose.
  - b) Wear double gloves tested for use with HDs and a disposable gown when handling a patient's body fluids after receiving HDs. Wear a face shield if splashing is possible (NIOSH, 2016).
  - c) For an incontinent patient, clean the patient's skin well with each diaper change. Apply a protective barrier ointment to the skin of the diaper area to decrease the chance of irritation from contact with drug metabolites (Polovich & Olsen, 2018).
  - d) Consider external urine collection devices for male and female incontinent patients to contain



the body fluid (e.g., condom catheters, external urine management systems).

- e) Flush the toilet with the lid down after disposing of excreta from a patient who has received HDs. Cover the open toilet with a plastic-backed pad to prevent splashing or release of aerosols during flushing when a lid is not present. No research supports the effectiveness of double flushing in reducing contamination, but this may be helpful with low-volume-per-flush toilets (Polovich & Olsen, 2018).
2. After radiopharmaceuticals (McQuestion et al., 2021)
  - a) Institute standard precautions (gloves and gown) when handling body fluids (e.g., sweat, saliva, urine, bowel movements, blood, semen, vaginal fluid). The duration of precautions varies depending on the radionuclide half-life.
  - b) Consult the radiation safety officer or nuclear pharmacist for precautions based on the specific radioisotope.
  - c) Education for patients and families is also recommended (McQuestion et al., 2021).

#### P. Handling patient linens

1. After HDs (Polovich & Olsen, 2018)
  - a) To the extent possible, preclude the need for laundering linens and clothing by using disposable linens or leakproof pads to contain HD-contaminated body fluids.
  - b) Handling of HD-contaminated bed linens and clothing while wearing PPE
    - (1) In the hospital setting
      - (a) Contaminated linens should be double bagged. Ensure the outer bag is leakproof.
      - (b) In most institutions, all linens are handled as contaminated by laundry personnel before washing.
    - (2) In the home setting (Polovich & Olsen, 2018)
      - (a) Wearing gloves, place contaminated linens into a washable pillowcase, and keep them separate from other items.
      - (b) Machine wash linens and cloth diapers twice with regular detergent and separately from other household items.
      - (c) Discard disposable diapers in plastic bags to prevent leakage.
      - (d) Discard used gloves in an HD waste container or household trash based on local requirements.
2. After radiopharmaceuticals: If body fluids are present, use standard precautions (gloves and barrier

gowns) when handling the linens of a patient who has received radiopharmaceuticals (McQuestion et al., 2021).

#### Q. Disposal of HDs and materials contaminated with HDs

1. In the hospital setting (NIOSH, 2004)
  - a) Place soft contaminated materials into a sealable, leakproof bag or a rigid hazardous waste container marked with a brightly colored label indicating the content's hazardous nature.
  - b) Use puncture-proof containers for sharp or breakable items. Dispose of needles and syringes intact; do not break or recap needles or crush syringes.
  - c) Seal containers when full.
  - d) Do not dispose of drug-contaminated items in infectious waste (red) containers. Some facilities autoclave these materials, which does not deactivate HDs (NIOSH, 2004; Smith, 2002).
  - e) Follow institutional policy regarding disposal of partial doses of HDs when administration is interrupted. Some drugs must be discarded as hazardous waste in designated containers if the container is not empty (Residues of Hazardous Waste in Empty Containers, 2011).
  - f) Only environmental services personnel who have received safe handling instructions should handle hazardous waste containers. Personnel should use PPE tested for use with HDs.
2. In the home setting (Polovich & Olsen, 2018)
  - a) Some agencies that provide HDs arrange for the proper disposal of contaminated equipment.
  - b) Designate an area where filled containers are placed for pickup, preferably locked and away from children and pets.
  - c) Follow county and state regulations regarding the disposal of HD waste.

#### R. Procedures following acute HD exposure

1. Accidents, improper technique, faulty equipment, or negligence in C-PEC operation can lead to exposure.
2. Initial interventions
  - a) In the event of skin exposure, remove any contaminated garments and immediately wash contaminated skin with soap and water. Refer to the SDS for agent-specific interventions.
  - b) In case of eye exposure, immediately flush the eye with saline solution or water for at least 15 minutes (ASHP, 2006), then seek emergency treatment. Areas where HDs are handled should have a sink with an eyewash station. Two functionally equivalent and cost-effective alternatives to an eyewash station are an IV bag of 0.9% sodium chloride solution connected to IV tubing or an irrigation bag of water or normal saline attached to the tubing to flush eyes (ASHP, 2006).

- c) In the event of inhalation exposure, move away from the area as quickly as possible. Depending on the severity of symptoms, seek emergency treatment from an employee health professional or emergency department. Refer to the SDS for agent-specific interventions.
  - d) For accidental ingestion, do not induce vomiting unless indicated in the SDS. Depending on the severity of symptoms, seek emergency treatment from an employee health professional or emergency department. Refer to the SDS for agent-specific interventions.
3. Reporting (Polovich & Olsen, 2018)
- a) Employee exposure: Report HD exposure to the employee health department or as institutional policy requires.
  - b) Patient exposure: Report HD exposure as institutional policy requires. In addition, inform the patient's healthcare providers.

#### S. Spill management

1. Spills result in contamination of the environment and are a source of exposure for healthcare workers and others; therefore, HD spills must be contained and cleaned up as soon as possible (USP, 2019). Even a small-volume spill should be considered a source of exposure and handled appropriately. Spill kits must be available wherever HDs are stored, transported, prepared, or administered, including the home setting (see Figure 12-2). Train those responsible for spill management in spill cleanup. Because a qualified person must be available for spill cleanup whenever HDs are handled (USP, 2019), many organizations train all HD handlers. Some facilities may designate a hazardous materials response team to clean up large spills (Occupational Safety and Health Standards, 2004). All workplaces should have standard

operating procedures that cover the essential points of spill management.

- a) All healthcare workers should wear PPE, which includes a gown tested for use with chemotherapy, when cleaning a spill or if there is a risk of spilling or splashing. If unavailable, use a lint-free gown made of a low-permeability fabric, such as polypropylene or other laminate materials; two pair of gloves tested for use with chemotherapy; face protection; and respiratory protection based on the drug. Face protection is required to prevent droplets from contacting the eyes. Respiratory protection is intended to prevent inhalation of powders, aerosols, or vapors.
- b) Assess the exposure of any individuals involved and isolate them from the spill. If an individual's skin or clothing has contacted the HD, immediately remove the contaminated clothing and wash with soap and water. Additional personnel trained in the safe handling of HDs can assist the exposed individual while others attend to the spill.
- c) Spill kits should be located in all areas where HDs are routinely handled and if HDs are being prepared or administered in a nonroutine area. Keep others out of the area during cleanup and, if possible, have a second trained person assist with holding the spill waste disposal bag.
- d) Wear a NIOSH-approved respirator appropriate for the spilled agent (OSHA, 2016). This may include a PAPR if the capacity of the spill kit is exceeded or if airborne exposure to vapors or gases is known or suspected.
- e) Use items in the spill kit to contain the spill, such as absorbent pads, cloths, or spill control pillows.
- f) Clean up the spill according to its location and type. Access the SDS for the spilled agent to determine if a deactivator is recommended.
- g) Begin with the least-contaminated area and finish with the most-contaminated area to prevent spreading the spilled drug to noncontaminated areas.
- h) Rinse the area with water and then clean with detergent, sodium hypochlorite solution, neutralizer, or other validated decontamination solution (Power & Coyne, 2018).
- i) Rinse the area with plain water several more times. Adequate dilution of HD residue is necessary to ensure that the drug and any chemical residue have been removed and transferred to the wipes.
- j) Discard all material used in cleanup in an HD waste bag. Seal the waste bag and place it in a puncture-proof container designated for HD waste.
- k) After handling and disposal of HDs, remove the outer gloves, turning them carefully inside

**FIGURE 12-2.** Contents of an Antineoplastic Spill Kit

- 2 pairs of disposable gloves that have been tested for use with hazardous drugs
- Disposable, chemical-resistant gowns (with back closure)
- Chemical-resistant shoe covers
- Chemical splash goggles
- National Institute for Occupational Safety and Health–approved respirator masks
- Absorbent, plastic-backed sheets or spill pads
- At least 2 sealable thick plastic hazardous waste disposal bags with an appropriate warning label
- A puncture-resistant container

This may not include everything needed in the event of a spill (e.g., other items may be specific to the homecare environment/carpeting). Some contents degrade or expire over time. It may make sense to make custom kits for those on spill response teams with an appropriate, fit-tested mask.

*Note.* Based on information from American Society of Health-System Pharmacists, 2006; Polovich & Olsen, 2018.

out to avoid touching the outside. When doffing PPE, remove outer gloves, gown, shoe covers (if used), and inner gloves; wash hands with soap and water; don clean gloves; and remove mask and face shield (if used). Remove gloves and rewash hands.

- l) In the event a PAPR or chemical cartridge mask is used, a clean pair of gloves should be worn to remove the PAPR/cartridge mask, and it should be placed on a plastic-backed pad. Gloves should then be removed and hands washed. A final pair of gloves would be needed to clean the equipment per the manufacturer's guidelines. After, the gloves should be removed and hands washed again.
- m) Carpeting should be avoided in patient care settings. Several studies have documented bacterial growth and persistence in carpeting, and it is impossible to decontaminate an HD spill on carpeting (Centers for Disease Control and Prevention, 2019). If a spill occurs on carpeting (more likely in the home setting), whoever cleans the spill should don PPE and appropriate respiratory protection. An absorbent powder should be used, and the area should be vacuumed to remove the dried powder. A vacuum used in spill cleanup should be equipped with a HEPA filter to contain the HD-contaminated absorbent powder and limit further environmental contamination (Polovich & Olsen, 2018).
- n) All previous entries apply to the home setting; however, after donning PPE, dishwashing or laundry detergent and water with disposable cloths or paper towels are the recommended cleaning agents, followed by water with disposable towels. All used towels should go in a plastic bag with the used PPE. That bag should go in a second bag. Any linen or clothing that came into contact with the spill should be washed separately from other laundry. The home health nurse, clinic, or doctor's office should be called promptly to report the spill and provide guidance on using the spill kit. They will let the patient know about the need to replace the spilled drug to complete treatment. They will also arrange to pick up the waste material or tell the patient or caregiver where to bring it for proper disposal (Polovich & Olsen, 2018).
- o) Cleaning up a spill in a biosafety cabinet or compounding aseptic containment isolator (ASHP, 2006)
  - (1) Clean the spill according to the guidelines for a spill. Complete cleanup by rinsing the surface with a sterile water rinse (Polovich & Olsen, 2018).

- (2) Include the drain spillage trough in the cleaning and decontamination efforts.
- (3) If the spill contaminated the HEPA filter, seal the open front of the biosafety cabinet in plastic. Label any C-PEC as contaminated equipment. Schedule a C-PEC service technician to change the HEPA filter. Ensure that the C-PEC is not used before the filter is replaced.

- p) Cleaning up a spill in the home setting (see Figure 12-1)
- q) Report and document HD spills according to institutional policy. For any spill, complete a report about the spill and forward it to those specified by institutional policy (ASHP, 2006). Document the following:
  - (1) Name of the drug
  - (2) Approximate volume of the spill
  - (3) How the spill occurred
  - (4) The spill management procedures followed
  - (5) The names of personnel, patients, and others exposed to the spill
  - (6) A list of personnel notified of the spill

2. In the case of a spill of a radiolabeled mAb or contamination with the radioactive body fluid of a patient recently treated with radiopharmaceuticals, perform the following (McQuestion et al., 2021):
  - a) In case of contact with skin or eyes, the affected area should be flushed immediately with water.
  - b) In the event of spillage of radiopharmaceuticals, the radiation safety officer should be contacted immediately to initiate the necessary measurements and required procedures to decontaminate the area. To remove the contamination, a complexing agent, such as ethylenediaminetetraacetic acid (EDTA) solution, is recommended.
  - c) Protective shields for needles and containers must be used.
  - d) Clinicians must observe local regulations for procedures involving unsealed radioactive resources.
  - e) Use of 1 cm thick acrylic glass or lead-loaded acrylic glass shields during labeling is required.
  - f) Forceps and tongs should be used as gripping tools.
  - g) Plastic gloves, disposable waterproof gowns, and acrylic glass eye protection should be used.

#### T. Requirements for policies regarding the handling of HDs

1. Occupational Safety and Health Standards (2004) require that employers provide a safe and healthful workplace. Employers must implement policies and procedures related to the safe handling of HDs. Policies should address all aspects of handling these hazardous chemicals to protect employees, patients, families, and the environment from contamination.

2. Such policies must do the following (NIOSH, 2004; USP, 2019):
  - a) Outline procedures to ensure the safe storage, transport, administration, and disposal of hazardous agents.
  - b) Describe the procedure for identifying new HDs and updating the list of HDs used in the facility.
  - c) Require that all employees who handle HDs wear PPE.
  - d) Mandate that HDs be prepared in a biosafety or compounding aseptic containment isolator (USP, 2019).
  - e) Prohibit staff from eating, drinking, smoking, chewing gum, using tobacco, storing food, and applying cosmetics in areas where HDs are prepared or administered.
  - f) Mandate initial training for all employees who prepare, transport, or administer HDs or care for patients receiving these drugs prior to assuming these responsibilities and require documented personnel competency at least annually (USP, 2019).
  - g) Require training to include the risks of exposure and appropriate procedures for minimizing exposure; the policy should describe how training is documented (OSHA, 2012; USP, 2019).
  - h) Require that documents such as SDSs are available to healthcare workers who handle HDs.
  - i) Describe the procedures for the management of HD spills.
  - j) Set forth a plan for medical surveillance of personnel handling HDs.
  - k) Ensure that employees of reproductive capability acknowledge in writing that they have been informed of the risks of HD exposure around pregnancy (USP, 2019).
  - l) Address HD handling for workers who are actively trying to conceive or who are pregnant or breastfeeding.
    - (1) Even when all recommended precautions are used, the potential for accidental exposure cannot be eliminated.
    - (2) Developing fetuses and newborn infants may be more susceptible to harm from certain HDs. Therefore, an additional level of protection is recommended for those most vulnerable to the reproductive and developmental effects of HDs (Connor et al., 2014).
    - (3) Degree of risk to the employee is difficult to quantify and may be based on length of and type of exposure, adoption of full PPE recommendations, and use of closed-system drug-transfer devices and other engineering and administrative controls associated with safe handling.
    - (4) Institutional policy should describe the process for requesting accommodation, options available to staff members, and the ability of the institution to provide an alternative assignment. Where feasible, employees who request alternative duty for one of the noted conditions should be provided with responsibilities that do not include the handling of HDs. The ability of an employer to provide alternative duty is fluid and may vary based on census, staffing, or other factors. Whenever possible, the Oncology Nursing Society supports the provision of alternative duty to reduce risk of adverse health outcomes in individuals who are pregnant, breastfeeding, or trying to conceive and supports high level institutional strategies to operationalize fulfilling alternative assignment requests for these individuals (Oncology Nursing Society & Hematology/Oncology Pharmacy Association, 2019).
    - (5) The employee is responsible for notifying the employer of the specific situation (e.g., preconception, pregnancy, breastfeeding). The American College of Occupational and Environmental Medicine provides guidelines for reproductive hazard management (Meyer et al., 2016).
    - m) Define quality improvement programs that monitor compliance with safe handling policies and procedures.

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## CHAPTER 13

# Infusion-Related Complications

A. Complications during or shortly after parenteral administration of cancer treatment (Gill et al., 2018; Gorski et al., 2021; Kreidieh et al., 2016)

1. Infiltration: passage or escape of intravenously administered drugs into the tissue
2. Vesicant extravasation: inadvertent leakage of drugs capable of causing tissue damage into the subcutaneous or subdermal tissue or other unintended sites (e.g., pleural space)
3. Irritation: a localized inflammatory reaction at the infusion or injection site
4. Flare reaction: a local allergic reaction along a vein caused by irritating drugs
5. Infusion reactions: reactions mediated by the immune system (e.g., hypersensitivity, anaphylaxis, cytokine release syndrome [CRS])

B. Extravasation of vesicants resulting in potential tissue damage

1. Pathophysiology: occurs as a result of one of two primary mechanisms
  - a) DNA-binding vesicants: The vesicant binds to nucleic acids in the DNA of healthy cells in the tissue, causing cell death. The dead cells release complexes taken up by adjacent healthy cells. The cellular uptake of extracellular substances creates a continuing cycle of tissue damage as the DNA-binding vesicant is retained and recirculated in the tissue for an extended period (Luedke et al., 1979). DNA-binding vesicants include anthracyclines (e.g., daunorubicin, doxorubicin, epirubicin, idarubicin), dactinomycin, mitomycin C, mitoxantrone, and trabectedin (Chang, 2020; Kreidieh et al., 2016; Theman et al., 2009).
  - b) Non-DNA-binding vesicants: The vesicant does not bind to cellular DNA and has an indirect effect on cells in healthy tissue (e.g., nonphysiologic pH, nonphysiologic osmolarity) (Ong & Van Gerpen, 2020). These vesicants are eventually metabolized in the tissue and are more easily neutralized than DNA-binding vesicants (Ener et al.,

2004). Examples of non-DNA-binding vesicants include plant alkaloids (e.g., vinblastine, vincristine, vindesine, vinorelbine) and taxanes, which as a group, have usually been classified as mild vesicants. Examples of taxanes include the following (Ener et al., 2004; Schrijvers, 2003; Stanford & Hardwicke, 2003):

- (1) Cabazitaxel infiltration has not caused skin or tissue impairment based on clinical trials and postmarketing reports at the time of this writing (Sanofi-Aventis U.S., 2021a).
- (2) Docetaxel extravasation may cause hyperpigmentation, erythema, and tenderness (Sanofi-Aventis U.S., 2021b).
  - (a) In a case report, erythema with significant swelling and accompanying reduction of arm range of motion was noted on the day following docetaxel extravasation from an implanted port. Despite dexamethasone and chlorpheniramine treatment, erythema progressed to  $18 \times 15$  cm in size one week later (Chang et al., 2014).
  - (b) Su et al. (2020) described bullous lesions following the venous tract after docetaxel extravasation.
  - (c) Another case study showed treatment with intralesional steroids hastened cutaneous resolution after peripheral extravasation of docetaxel (Roman et al., 2017).
  - (d) Recall dermatitis at a previous docetaxel extravasation site, occurring during subsequent docetaxel administration in another location, also has been reported (Kramer et al., 2011).
- (3) Paclitaxel injection site reactions, including reactions secondary to extravasation,

are usually mild and consist of erythema, tenderness, skin hyperpigmentation, or swelling at the injection site. These reactions have been observed more frequently with 24-hour infusions than 3-hour infusions.

- (a) Recurrence of skin reactions at a site of previous extravasation following administration of paclitaxel injection at a different site (recall reactions) has been reported.
- (b) More severe events, such as phlebitis, cellulitis, induration, skin exfoliation, necrosis, and fibrosis, have been reported. In some cases, onset occurred during a prolonged infusion or was delayed by 7–10 days (Hospira, 2021d).
- (c) Most clinical reports of paclitaxel extravasation were published in the first few years following its U.S. Food and Drug Administration approval and were reviewed by Stanford and Hardwicke (2003). They concluded that paclitaxel was a “mild vesicant” (p. 276).
- (d) Data suggest that the potential for tissue damage is dependent on paclitaxel concentration and infusion duration (Barbee et al., 2014).
- (4) Docetaxel and paclitaxel have also been classified as exfoliants, or drugs that may cause skin inflammation and peeling, without causing the underlying tissue death that typically occurs with true vesicants (Kreidieh et al., 2016).
- (5) Phlebitis, cellulitis, induration, fibrosis, and necrosis following extravasation of paclitaxel protein-bound particles for injectable suspension (Abraxane®) have been identified with postapproval use and reported to the manufacturer. In some cases, the onset of symptoms occurred during a prolonged infusion or was delayed by 7–10 days.
- (6) The available published literature supports the safety of IV administration of taxanes at recommended concentrations and durations using peripheral venous access (Barbee et al., 2014). However, some patients may require central venous access device (VAD) insertion for taxane administration (Jackson-Rose et al., 2017). In some institutions, paclitaxel may be admin-

istered for longer than 60 minutes through a peripheral line on an infusion pump. Institutions should establish monitoring procedures to minimize the risk of extravasation. Peripheral infusion of taxanes requires diligent monitoring of the site by nurses and engagement of patients to report any signs or symptoms of infiltration.

2. Factors affecting tissue damage severity following vesicant extravasation (Schulmeister, 2011)
  - a) Type of vesicant extravasated: DNA-binding vesicants cause greater tissue damage than non-DNA-binding vesicants.
  - b) Concentration and amount of vesicant in the tissue: Higher concentration or greater volume causes more damage.
  - c) Location of extravasation: Areas with little subcutaneous tissue and those overlying veins, arteries, and nerves are more likely to have more significant damage.
  - d) Patient factors: Older age, comorbidity (e.g., diabetes), and impaired immunocompetence are factors.
3. Risk factors for peripheral extravasation (Gorski et al., 2021)
  - a) Small, fragile veins
  - b) Previous multiple venipunctures
  - c) Sensory deficits in the area of the VAD or patients with communication deficits to verbalize or convey pain, tightness, or other discomforts (Gorski et al., 2021)
  - d) Application of topical skin numbing agents prior to venipuncture, which decreases sensation at and around the venipuncture site
  - e) Limited vein selection because of lymph node dissection, lymphedema, or limb removal
  - f) Impaired cognition, altered mental status (impairs ability to detect administration site sensation changes), or somnolence
  - g) Probing during IV catheter insertion
  - h) Inadequately secured IV catheter
  - i) Administration site in areas prone to movement (e.g., wrist, antecubital area)
  - j) Use of rigid IV devices (e.g., steel-winged butterfly needles)
  - k) Prior treatment with irritating or sclerosing drugs, such as chemotherapy
  - l) Administration of a vesicant peripherally when the manufacturer stipulates it should be administered via a central line, such as trabectedin (Janssen Biotech, 2020b) or daunorubicin and cytarabine liposome (Jazz Pharmaceuticals, 2021). Data suggest that trabectedin can be safely administered via a central venous

- catheter, such as a peripherally inserted central catheter (PICC), or other central VADs, such as an implanted port (Martella et al., 2015).
- m) Female sex (Gorski et al., 2021)
  - n) Current infection (Gorski et al., 2021)
4. Possible etiologies of peripheral extravasations (Sauerland et al., 2006)
    - a) Vein wall puncture, piercing, or trauma
    - b) Dislodgment of the catheter from the vein
    - c) Administration of a vesicant in a vein below a recent (less than 24 hours) venipuncture site
    - d) Administration of a vesicant in a vein below a recent or non-healed vesicant extravasation site
    - e) Inadvertent intramuscular or subcutaneous vesicant administration
    - f) Insufficient catheter length inserted into the vein, increasing the chance of extravasation with movement
  5. Risk factors for extravasation from central VADs (Sauerland et al., 2006)
    - a) Difficulty encountered during device insertion (e.g., probing during venipuncture, inability to advance guidewire or catheter)
    - b) Inadvertent slicing, piercing, or nicking of the catheter prior to or during insertion
    - c) Device misplacement with catheter tip outside of the venous system
    - d) Insufficient length of noncoring needle (implanted port)
    - e) Inadequately secured noncoring needle (implanted port)
    - f) Presence of a fibrin sheath or thrombus at the catheter tip
    - g) Catheter migration
    - h) Long dwell time of catheters inserted using a subclavian approach, in which the catheter is placed between the clavicle and first rib; increases the risk of catheter fracture secondary to compression or pinch-off
  6. Possible etiologies of extravasations from central VADs (Gibson & Bodenham, 2013; Goossens et al., 2011; Sauerland et al., 2006)
    - a) Inadvertent misplacement of catheter tip outside of the venous system (e.g., pleural space) during the insertion procedure
    - b) Vein perforation during insertion
    - c) Postinsertion vein erosion
    - d) Catheter leakage, rupture, or fracture
    - e) Separation of the catheter from a portal body (implanted port)
    - f) Incomplete insertion of a noncoring needle into an implanted port
    - g) Noncoring needle dislodgment from an implanted port
    - h) Backflow of vesicant along the catheter to the venotomy site secondary to fibrin sheath or thrombus at the catheter tip
  7. Signs and symptoms of vesicant extravasation (see Table 13-1, Appendix H)
    - a) Vein irritation and flare reactions may mimic some of the signs and symptoms of vesicant extravasation.
    - b) Vein irritation and flare reactions are unique to peripheral chemotherapy administration; they do not occur when chemotherapy is administered via central VADs because the chemotherapy is rapidly diluted in large veins (Wickham et al., 2006). However, vesicant extravasation can occur from a central VAD due to inadvertent catheter tip placement outside the venous system or erosion of the vein wall. It may cause chest pain, shortness of breath, and shock secondary to blood loss (Gibson & Bodenham, 2013). Criteria for adverse events from infusion site extravasation are found in Table 13-2.
    - c) Additional signs and symptoms of vesicant extravasation (Ener et al., 2004; Jackson-Rose et al., 2017; Pérez Fidalgo et al., 2012)
      - (1) IV flow rate that slows or stops
      - (2) Resistance during IV bolus (push) vesicant administration
      - (3) Leaking around the IV catheter or implanted port needle
      - (4) Loss of blood return
  8. Possible consequences of untreated vesicant extravasation (Goolsby & Lombardo, 2006; Pérez Fidalgo et al., 2012)
    - a) Blistering, usually beginning within three to five days
    - b) Peeling and sloughing of skin, usually beginning within two weeks after extravasation
    - c) Tissue necrosis, usually evident two to three weeks after extravasation
      - (1) DNA-binding vesicants remain in the tissue for long periods. The area of tissue necrosis becomes progressively larger and deeper over time.
      - (2) Non-DNA-binding vesicants are more easily metabolized in the tissue. Tissue necrosis is generally localized and improves over time.
    - d) Damage to tendons, nerves, and joints
    - e) Functional and sensory impairment of the affected area
    - f) Disfigurement
    - g) Loss of limb (rare)
  9. Vesicant extravasation management: A suspected vesicant extravasation is best assessed and managed using a systematic and collaborative approach that

**TABLE 13-1.** Signs and Symptoms of Infusion-Related Venous Complications

| Sign or Symptom | Vesicant Infiltration and Extravasation                                                                                                                                                                                                                                                                                   | Venous Irritation                                                                                     | Flare Reaction                                                                                                                      |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|
| Blood return    | Immediate: Loss of blood return from IV devices usually occurs.                                                                                                                                                                                                                                                           | Blood return should be present. If loss of blood return occurs, suspect infiltration of irritant.     | Blood return is present.                                                                                                            |
| Pain            | Immediate: Pain typically occurs and is described as burning, stinging, or a sensation of coolness at and around the vesicant administration site. However, some patients do not experience pain when a vesicant extravasates.<br>Delayed: Pain usually increases in intensity over time.                                 | Aching and tightness along a peripheral vein occur as the drug infuses above the administration site. | No pain occurs; the skin overlying or above the vein may itch.                                                                      |
| Redness         | Immediate: Redness in the area of the vesicant administration site commonly occurs but is not always present or may be difficult to detect if the extravasation is occurring deeper in the tissue (e.g., as a result of needle dislodgment from the implanted port).<br>Delayed: Redness generally intensifies over time. | The vein may appear red-dened or darkened.                                                            | Immediate blotches or streaks develop along the vein, which usually subside within a few minutes. Wheals may appear along the vein. |
| Swelling        | Immediate: Swelling is commonly observed and is easier to detect when extravasation is superficial (e.g., from a peripheral vein) rather than deep in the tissue (e.g., implanted ports).<br>Delayed: Swelling typically increases over time.                                                                             | Swelling does not occur.                                                                              | Swelling does not occur.                                                                                                            |
| Ulceration      | Immediate: Skin integrity is intact.<br>Delayed: If vesicant extravasation is not treated, blistering and sloughing begin within 1–2 weeks, followed by tissue necrosis that may require surgical debridement and skin grafting or flap placement.                                                                        | Ulceration does not occur.                                                                            | Ulceration does not occur.                                                                                                          |

Note. Based on information from Goolsby & Lombardo, 2006; Gorski et al., 2021; Sauerland et al., 2006; Wickham et al., 2006.

involves the patient, the nurse administering the vesicant, and the prescribing provider.

- a) Initial management of extravasation: Assess the site and patient symptoms at the first sign of extravasation, during the time the IV device is assessed, and after initial management.
- b) Steps to take when vesicant extravasation occurs or is suspected (Goolsby & Lombardo, 2006; Schulmeister, 2011)

- (1) Immediately stop administering the vesicant and IV fluids.
- (2) Disconnect the IV tubing from the IV device. Do not remove the IV device or noncoring port needle.
- (3) Attempt to aspirate residual vesicant from the IV device or port needle using a small (1–3 ml) syringe.
- (4) Remove the peripheral IV device or port needle.

**TABLE 13-2.** Common Terminology Criteria for Adverse Events Grading for Infusion Site Extravasation

| Adverse Event               | Grade          |                                                                              |                                                                                |                                                              |       |
|-----------------------------|----------------|------------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------|-------|
|                             | 1              | 2                                                                            | 3                                                                              | 4                                                            | 5     |
| Infusion site extravasation | Painless edema | Erythema with associated symptoms (e.g., edema, pain, induration, phlebitis) | Ulceration or necrosis, severe tissue damage; operative intervention indicated | Life-threatening consequences; urgent intervention indicated | Death |

Note. From *Common Terminology Criteria for Adverse Events* [v.5.0], by National Cancer Institute Cancer Therapy Evaluation Program, 2017 ([https://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/docs/CTCAE\\_v5\\_Quick\\_Reference\\_5x7.pdf](https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf)). In the public domain.

- (5) Initiate appropriate management measures found in Table 13-3 and institutional policies.
- c) Vesicant extravasation antidotes and treatments

- (1) The efficacy of extravasation antidotes and treatments is unknown. One exception is dexrazoxane for injection, which has 98.2% overall efficacy for treating anthracycline extravasation (Mouridsen et al., 2007).

**TABLE 13-3.** Vesicant Extravasation Management Guidelines

| Classification/Drug                                                                                                                                                       | Immediate Topical Therapy                                                                                                                                        | Administration, Monitoring, and Follow-Up                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Alkylating agent (DNA binding)<br>• Lurbinectedin (Zepzelca)<br>• Trabectedin (Yondelis®)                                                                                 | Cold<br>Apply cold pack for 15–20 minutes at least 4 times a day for the first 24 hours.                                                                         | Assess the extravasation area for pain, blister formation, and skin sloughing as needed or per institutional policy.<br>In collaboration with the provider, refer patients for specialized care when indicated or needed (e.g., plastic or hand surgery consult, physical therapy, pain management, rehabilitation services).<br>(Janssen Biotech, 2020b; Jazz Pharmaceuticals, 2022)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Anthracenedione (DNA binding)<br>• Mitoxantrone                                                                                                                           | Cold<br>Apply cold pack for 15–20 minutes at least 4 times a day for the first 24 hours.                                                                         | Extravasation typically causes a blue discoloration of the infusion site area and may require debridement and skin grafting.<br>Assess the extravasation area for pain, blister formation, and skin sloughing as needed or per institutional policy.<br>In collaboration with the provider, refer patients for specialized care when indicated or needed (e.g., plastic or hand surgery consult, physical therapy, pain management, rehabilitation services).<br>(Chang, 2020; Hospira, 2021c)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Antitumor antibiotics: anthracyclines (DNA binding)<br>• Daunorubicin (Cerubidine®)<br>• Doxorubicin (Adriamycin®)<br>• Epirubicin (Ellence®)<br>• Idarubicin (Idamycin®) | Cold<br>Apply cold pack for 15–20 minutes at least 4 times a day for the first 24 hours.<br>Remove cold pack at least 15 minutes prior to dexrazoxane treatment. | Antidote: dexrazoxane for injection<br>• Mechanism of action: unknown<br>• Dose: The recommended dose is based on body surface area.<br>– Day 1: 1,000 mg/m <sup>2</sup><br>– Day 2: 1,000 mg/m <sup>2</sup><br>– Day 3: 500 mg/m <sup>2</sup><br>– The maximum recommended dose is 2,000 mg on days 1 and 2 and 1,000 mg on day 3. The dose should be reduced 50% in patients with creatinine clearance values < 40 mL/min.<br>• Preparation: Each 500 mg vial of dexrazoxane must be mixed with 50 mL diluent. The patient's dose is then added to a 1,000 mL lactated ringers infusion bag for administration.<br>• Storage: Store at room temperature between 15°C–30°C (59°F–86°F).<br>• Initiate the first dexrazoxane infusion as soon as possible and within 6 hours of the anthracycline extravasation.<br>• Infuse dexrazoxane over 1–2 hours in a large vein in an area other than the extravasation area (e.g., opposite arm). The same arm should be used only when the patient's clinical status (e.g., lymphedema, loss of limb) precludes the unaffected arm, and a large vein above the extravasation site should be used for dexrazoxane administration.<br>• Dimethyl sulfoxide should NOT be applied to the extravasation area.<br>Assess the extravasation area for pain, blister formation, and skin sloughing as needed or per institutional policy.<br>Instruct patients to monitor the extravasation site and report fever, chills, blistering, skin sloughing, and worsening pain.<br>Instruct patients with peripheral extravasations to report arm or hand swelling and stiffness.<br>Instruct patients about treatment side effects (e.g., nausea, vomiting, diarrhea, stomatitis, bone marrow suppression, elevated liver enzyme levels, and infusion site burning).<br>Monitor complete blood count and liver enzyme levels.<br>(Clinigen, 2020) |

(Continued on next page)

**TABLE 13-3.** Vesicant Extravasation Management Guidelines (*Continued*)

| Classification/Drug                                                                                                                                                                                                                                                                      | Immediate Topical Therapy                                                                   | Administration, Monitoring, and Follow-Up                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Antitumor antibiotics: miscellaneous (DNA binding) <ul style="list-style-type: none"> <li>• Dactinomycin (actinomycin D, Cosmegen<sup>®</sup>)</li> <li>• Daunorubicin and cytarabine liposome (Vyxeos<sup>®</sup>)</li> <li>• Mitomycin C (Mutamycin<sup>®</sup>)</li> </ul>            | Cold<br>Apply cold pack for 15–20 minutes at least 4 times a day for the first 24 hours.    | Assess the extravasation area for pain, blister formation, and skin sloughing as needed or per institutional policy. In collaboration with the provider, refer patients for specialized care when indicated or needed (e.g., plastic or hand surgery consult, physical therapy, pain management, rehabilitation services).<br>(Accord Biopharma, 2017; Jazz Pharmaceuticals, 2021; Lundbeck, 2012)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Microtubule inhibitors: taxanes (non-DNA binding) <ul style="list-style-type: none"> <li>• Cabazitaxel (Jevtana<sup>®</sup>)</li> <li>• Docetaxel (Taxotere<sup>®</sup>)</li> <li>• Paclitaxel (Taxol<sup>®</sup>)</li> <li>• Paclitaxel protein-bound (Abraxane<sup>®</sup>)</li> </ul> | Cold<br>Apply cold pack for 15–20 minutes at least 4 times a day for the first 24 hours.    | Assess the extravasation area for pain, blister formation, and skin sloughing as needed or per institutional policy. Instruct patients to monitor the extravasation site and to report fever, chills, blistering, skin sloughing, and worsening pain. Instruct patients with peripheral extravasations to report arm or hand swelling and stiffness.<br>(Bristol-Myers Squibb, 2021b; Hospira, 2021d; Sanofi-Aventis, 2021a, 2021b)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Vinca alkaloids (non-DNA-binding) <ul style="list-style-type: none"> <li>• Vinblastine</li> <li>• Vincristine</li> <li>• Vinorelbine tartrate (Navelbine<sup>®</sup>)</li> </ul>                                                                                                         | Heat<br>Apply warm pack for 15–20 minutes at least 4 times a day for the first 24–48 hours. | Antidote: hyaluronidase <ul style="list-style-type: none"> <li>• Mechanism of action: degrades hyaluronic acid and promotes drug dispersion and absorption</li> <li>• Dose: Administer 150 units of the hyaluronidase solution as 5 separate injections, each containing 0.2 ml of hyaluronidase, subcutaneously into the extravasation site using a 25-gauge or smaller needle (change needle with each injection).</li> <li>• Preparation: Prepare per package insert. Do not dilute. Use the solution as provided.</li> </ul> Assess the extravasation area for pain, blister formation, and skin sloughing as needed or per institutional policy. Instruct patients to monitor the extravasation site and report fever, chills, blistering, skin sloughing, and worsening pain. Instruct patients with peripheral extravasations to report arm or hand swelling and stiffness.<br>(Fresenius Kabi, 2016; Hospira, 2013; Kreidieh et al., 2016; Pierre Fabre Pharmaceuticals, 2020) |
| Vinca alkaloids: miscellaneous (non-DNA-binding) <ul style="list-style-type: none"> <li>• Liposome-encapsulated vincristine (Mariqibo<sup>®</sup>)</li> </ul>                                                                                                                            | Heat<br>Apply warm pack for 15–20 minutes at least 4 times a day for the first 24–48 hours. | If extravasation is suspected, discontinue infusion immediately and consider local treatment measures. Assess the extravasation area for pain, blister formation, and skin sloughing as needed or per institutional policy. Instruct patients to monitor the extravasation site and to report fever, chills, blistering, skin sloughing, and worsening pain. Instruct patients with peripheral extravasations to report arm or hand swelling and stiffness.<br>(Acrotech Biopharma, 2020)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

(2) In two European studies, 53 of 54 patients with biopsy-confirmed anthracycline extravasation did not require surgical intervention after receiving dexrazoxane administered via IV daily for three days. The median baseline extravasation area was 25 cm<sup>2</sup> (range 1–253 cm<sup>2</sup>), and 11 patients had extravasation areas exceeding 75 cm<sup>2</sup>. Thirteen patients had late sequelae at the extravasation site, such as pain, fibrosis, atrophy, and local sensory disturbance; all

were judged to be mild (Mouridsen et al., 2007).

- (3) A review conducted by Caballero Romero et al. (2018) noted positive outcomes in patients receiving dexrazoxane after extravasation of liposomal daunorubicin, pegylated liposomal doxorubicin, and liposomal doxorubicin.
- (4) No clinical trials have been conducted to determine the efficacy of dimethyl sulfide, sodium thiosulfate, hyaluronidase,



growth factors, early surgical intervention, saline washout or flushing, hyperbaric oxygen, or 3% solution of boric acid in treating biopsy-confirmed vesicant extravasations from peripheral IV catheters and implanted ports. Information about these antidotes and treatments is anecdotal and based on case reports.

- (5) Use of hyaluronidase for vinca alkaloid extravasation is recommended by package inserts and supported by case reports (Bertelli et al., 1994; Kreidieh et al., 2016; Maly et al., 2018; Pluschnig et al., 2015; Schrijvers, 2003). Hyaluronidase treatment is generally recommended within one hour of extravasation (Maly et al., 2018; Rubach, 2018). Topical heat is recommended to help disperse (Firat et al., 2013; Pluschnig et al., 2015; Rubach, 2018; Schrijvers, 2003).
  - (6) Limited data and conflicting case studies exist for using hyaluronidase for taxane extravasation.
    - (a) Du Bois et al. (1996) found patients with paclitaxel extravasations treated with hyaluronidase took longer to recover than those without and suggested cold therapy alone.
    - (b) Schrijvers (2003) noted a mouse study in which hyaluronidase after paclitaxel extravasation prevented ulceration.
    - (c) Pérez Fidalgo et al. (2012) recommended hyaluronidase with taxanes with limited evidence (Level V-C).
    - (d) Kimmel et al. (2018) discouraged hyaluronidase plus heat for taxanes and recommended cold alone.
  - (7) Anecdotal reports of treatment of peripheral and central VAD anthracycline extravasations with IV dexrazoxane administered as directed suggest efficacy in mitigating anthracycline-induced tissue damage (Araque Arroyo et al., 2010; Conde-Estévez et al., 2010; Fontaine et al., 2012; Langer, 2007, 2008; Uges et al., 2006). In a case report of IV dexrazoxane administration 72 hours after peripheral epirubicin extravasation (and after being initially treated with topical dimethyl sulfoxide 99%), the patient had complete recovery without any sequelae (Aigner et al., 2014).
  - (8) Anecdotal reports of treatment of intracavitary anthracycline vesicant extravasations include saline washout of the pleural space with concurrent IV dexrazoxane administration (Chang & Murray, 2016) and video-assisted thoracoscopy (to visualize tissue damage) followed by thoracoscopic-assisted pleural lavage with periprocedural IV infusion of dexrazoxane (Aguirre et al., 2017).
  - (9) A case report described liposomal doxorubicin extravasation initially treated conservatively with cold compresses on the affected arm. Three days later, when the pain worsened and skin redness increased, the patient was treated with IV dexrazoxane and completely recovered (de Vos et al., 2012).
  - (10) In a study by Onesti et al. (2017), saline washout and topical corticosteroids after extravasation in 545 patients prevented ulceration in 373 cases (Onesti et al., 2017). Taibi et al. (2020) found that five patients that underwent subcutaneous washout with saline exclusively had no necrosis and less delay in the resumption of treatment than two patients without saline washout. One case study suggested that saline washout may be helpful for oxaliplatin extravasation (Bahadori & Demiray, 2018).
10. Documentation of vesicant extravasation and treatment: Key elements for inclusion in vesicant extravasation documentation are listed in Figure 13-1. Appendix I includes an example of a vesicant drug extravasation record.
  11. Patient follow-up: Dependent on individual patient needs and institutional policies
    - a) Periodically assess patient response to extravasation treatment.
      - (1) Assess patients receiving IV dexrazoxane on each day of the three-day treatment and again four to seven days after completing dexrazoxane treatment.
      - (2) Assess patients receiving other extravasation treatments (e.g., heat/cold, hyaluronidase) the day after the suspected extravasation and four to seven days later.
      - (3) Assessments can be done in person or via phone with photographs sent electronically per institutional policy.
      - (4) Reinforce patient teaching to notify the provider of worsening signs and symptoms.
    - b) Assessment may include inspection and measurement of the extravasation area, skin integ-

**FIGURE 13-1.** Key Elements of Vesicant Extravasation Documentation

- Date and time that extravasation occurred or was suspected
- Type and size of peripheral venous access device or type of central venous access device and gauge/length of noncoring needle (implanted ports)
- Location and patency of peripheral or central venous access device
- Number and location(s) of venipuncture attempts (for peripheral vesicant administration)
- Description and quality of blood return before and during vesicant administration
- Vesicant administration technique (e.g., bolus, infusion)
- Concentration and estimated amount of extravasated vesicant
- Symptoms reported by the patient (e.g., burning, pain)
- Description of administration site appearance, including measurement of edema or redness if present
- Photographs of administration site that include date and time in the photograph field (follow institutional guidelines when obtaining photographs from patients)
- Assessment of extremity (if applicable) for range of motion and discomfort with movement
- Immediate nursing interventions (e.g., topical cooling or warming, authorized prescriber notification)
- Extravasation antidote or treatment administered
- Follow-up recommendations (e.g., return appointments, referral for wound care)
- Patient teaching (e.g., assessing skin, monitoring temperature, reporting pain) and patient's response to teaching

*Note.* Based on information from Schulmeister, 2011.

riety, presence of pain or other symptoms, arm and hand mobility (for peripheral extravasations), and sensation.

- c) Obtain follow-up photographs that include or refer to the date and time taken per institutional policy.
- d) In collaboration with the provider, refer patients for specialized care when indicated (e.g., plastic or hand surgery consultation, physical therapy, wound team, pain management, rehabilitation services).
- e) Instruct patients to protect the extravasation area from sunlight, monitor the site, and report fever, chills, blistering, skin sloughing, and worsening pain.

### C. Irritation

1. Irritants: agents that may inflame and irritate peripheral veins during or after infusion
  - a) Examples include bleomycin, carboplatin, carmustine, dacarbazine, etoposide, 5-fluorouracil, gemcitabine, ifosfamide, liposomal daunorubicin, liposomal doxorubicin, streptozocin, and topotecan (Ener et al., 2004; Pérez Fidalgo et al., 2012; Sauerland et al., 2006).
  - b) Measures to reduce irritation during infusion

- (1) Increase dilution when possible and infuse with concurrent fluid administration.
  - (2) Administer via larger rather than smaller peripheral veins for peripheral infusions.
  - (3) Apply a warm pack to the administration site during infusion. As an exception, treat irritant liposomal anthracyclines (daunorubicin and doxorubicin) with topical cold application.
  - (4) Assess the administration site and monitor for pain, redness, and swelling in patients receiving irritating agents.
2. Irritants with vesicant properties: Agents that may inflame and irritate peripheral veins and can cause skin and tissue damage (e.g., blistering, sloughing) when higher concentrations or specific amounts of the drug inadvertently enter the tissue (see Table 13-4 for irritant infiltration management guidelines)
    - a) Bendamustine hydrochloride (Bendeka®)
      - (1) Postmarketing reports of infiltration include hospitalization for erythema, marked swelling, and pain; precautions should be taken to avoid extravasation (Teva Pharmaceuticals, 2020).
      - (2) Bendeka is prepared in a 50 ml infusion bag and administered over 10 minutes. The infusion site should be monitored for redness, swelling, pain, infection, and necrosis (Teva Pharmaceuticals, 2020). Concurrent IV fluids for peripheral administration may help reduce irritation during infusion and phlebitis noted in two recent case studies (Ajewole et al., 2019; Watanabe et al., 2013).
    - b) Immunotherapy agents: Although data on the infiltration of these agents are limited, antibodies are classified as irritants most likely because of their ability to cause local allergic reactions at the infusion site rather than direct cellular toxicity. Conjugated antibodies could have vesicant potential depending on their conjugate (Sallevet et al., 2020; Shafaei et al., 2017).
    - c) Immune checkpoint inhibitors (e.g., ipilimumab, nivolumab, pembrolizumab) possess an irritant potential and may cause thrombophlebitis (Pluschnig et al., 2016). However, Rodríguez-Alarcón and Conde-Estévez (2021) noted that infiltrations of two monoclonal antibodies, nivolumab and cetuximab, had no symptoms of extravasation.
    - d) Targeted agents: Local swelling and redness have been observed with infiltration of proteasome inhibitors (e.g., carfilzomib, ixazomib) (Pluschnig et al., 2016).

**TABLE 13-4.** Irritant Infiltration Management Guidelines

| Drug                                                                                                | Immediate Topical Therapy                                                                    | Administration, Monitoring, and Follow-Up                                                                                                                                                                                                                                                                                                                                                                                 |
|-----------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ado-trastuzumab emtansine (Kadcyla®)<br>• Irritant (usually)<br>• Vesicant (rarely)                 | Cold:<br>Apply cold pack for 15–20 minutes at least 4 times a day for the first 24–48 hours. | Assess the infiltration area for pain, blister formation, and skin sloughing as needed or per institutional policy.<br>Instruct patients to monitor the infiltration site and report fever, chills, blistering, skin sloughing, and worsening pain.<br>Instruct patients with peripheral extravasations to report arm or hand swelling and stiffness.<br>(Genentech, 2020a; Sallevelt et al., 2020; Shafaei et al., 2017) |
| Bendamustine hydrochloride (Bendeka®)<br>• Irritant (usually)<br>• Vesicant (rarely)                | Cold<br>Apply cold pack for 15–20 minutes at least 4 times a day for the first 24 hours.     | Assess the infiltration area for pain, blister formation, and skin sloughing as needed or per institutional policy.<br>Instruct patients to monitor the infiltration site and report fever, chills, blistering, skin sloughing, and worsening pain.<br>(Ajewole et al., 2019; Kreidieh et al., 2016; Teva Pharmaceuticals, 2020)                                                                                          |
| Bleomycin<br>• Irritant (usually)                                                                   | Cold<br>Apply cold pack for 15–20 minutes at least 4 times a day for the first 24 hours.     | Assess the infiltration area for pain, blister formation, and skin sloughing as needed or per institutional policy.<br>Instruct patients to monitor the infiltration site and report fever, chills, blistering, skin sloughing, and worsening pain.<br>(Hospira, 2021a)                                                                                                                                                   |
| Carboplatin (Paraplatin®)<br>• Irritant (usually)<br>• Vesicant (rarely)                            | Cold<br>Apply cold pack for 15–20 minutes at least 4 times a day for the first 24 hours.     | Assess the infiltration area for pain, blister formation, and skin sloughing as needed or per institutional policy.<br>Instruct patients to monitor the infiltration site and report fever, chills, blistering, skin sloughing, and worsening pain.<br>(Teva Pharmaceuticals, 2011)                                                                                                                                       |
| Carmustine (BiCNU®)<br>• Irritant (usually)                                                         | Cold<br>Apply cold pack for 15–20 minutes at least 4 times a day for the first 24 hours.     | The drug is also associated with burning at the injection site, although true thrombosis is rare.<br>Assess the infiltration area for pain, blister formation, and skin sloughing as needed or per institutional policy.<br>Instruct patients to monitor the infiltration site and report fever, chills, blistering, skin sloughing, and worsening pain.<br>(Heritage Pharmaceuticals, 2017)                              |
| Cisplatin (Platinol®)<br>• Irritant (usually)<br>• Vesicant (rarely) when concentration > 0.5 mg/ml | Cold<br>Apply cold pack for 15–20 minutes at least 4 times a day for the first 24 hours.     | Assess the infiltration area for pain, blister formation, and skin sloughing as needed or per institutional policy.<br>Instruct patients to monitor the infiltration site and report fever, chills, blistering, skin sloughing, and worsening pain.<br>(WG Critical Care, 2019)                                                                                                                                           |
| Dacarbazine<br>• Irritant (usually)                                                                 | Cold<br>Apply cold pack for 15–20 minutes at least 4 times a day for the first 24 hours.     | Assess the infiltration area for pain, blister formation, and skin sloughing as needed or per institutional policy.<br>Instruct patients to monitor the infiltration site and report fever, chills, blistering, skin sloughing, and worsening pain.<br>(Hospira, 2021b)                                                                                                                                                   |
| Enfortumab vedotin-ejtv (Padcev®)<br>• Irritant (usually)<br>• Vesicant (rarely)                    | Cold<br>Apply cold pack for 15–20 minutes at least 4 times a day for the first 24–48 hours.  | Assess the infiltration area for pain, blister formation, and skin sloughing as needed or per institutional policy.<br>Reactions may be delayed.<br>Instruct patients to monitor the infiltration site and report fever, chills, blistering, skin sloughing, and worsening pain.<br>(Astellas Pharma US, 2021; Rosenberg et al., 2019)                                                                                    |
| Etoposide (Etopophos®)<br>• Irritant (usually)                                                      | Heat<br>Apply warm pack for 15–20 minutes at least 4 times a day for the first 24–48 hours.  | Assess the infiltration area for pain, blister formation, and skin sloughing as needed or per institutional policy.<br>Instruct patients to monitor the infiltration site and report fever, chills, blistering, skin sloughing, and worsening pain.<br>(Bristol-Meyers Squibb, 2017)                                                                                                                                      |

(Continued on next page)

**TABLE 13-4.** Irritant Infiltration Management Guidelines (*Continued*)

| Drug                                                                                    | Immediate Topical Therapy                                                                                                                  | Administration, Monitoring, and Follow-Up                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|-----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 5-Fluorouracil<br>• Irritant (usually)                                                  | Cold<br>Apply cold pack for 15–20 minutes at least 4 times a day for the first 24 hours.                                                   | Assess the infiltration area for pain, blister formation, and skin sloughing as needed or per institutional policy.<br>Instruct patients to monitor the infiltration site and report fever, chills, blistering, skin sloughing, and worsening pain.<br>(Spectrum Pharmaceuticals, 2016)                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Gemcitabine (Gemzar®)<br>• Irritant (usually)                                           | Cold<br>Apply cold pack for 15–20 minutes at least 4 times a day for the first 24 hours.                                                   | Assess the infiltration area for pain, blister formation, and skin sloughing as needed or per institutional policy.<br>Instruct patients to monitor the infiltration site and report fever, chills, blistering, skin sloughing, and worsening pain.<br>(Eli Lilly and Company, 2019)                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Ifosfamide (Ifex®)<br>• Irritant (usually)                                              | Cold<br>Apply cold pack for 15–20 minutes at least 4 times a day for the first 24 hours.                                                   | Assess the infiltration area for pain, blister formation, and skin sloughing as needed or per institutional policy.<br>Instruct patients to monitor the infiltration site and report fever, chills, blistering, skin sloughing, and worsening pain.<br>(Baxter Healthcare, 2018)                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Irinotecan (Campostar®)<br>• Irritant<br>• Exfoliative dermatitis may occur.            | Cold<br>Flush the skin topically with sterile water and apply a cold pack for 15–20 minutes at least 4 times a day for the first 24 hours. | Assess the infiltration area for pain, blister formation, and skin sloughing as needed or per institutional policy.<br>Instruct patients to monitor the infiltration site and report fever, chills, blistering, skin sloughing, and worsening pain.<br>(Kreidieh et al., 2016; Pfizer, 2020)                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Loncastuximab tesirine-lpyl (Zynlonta®)<br>• Irritant (usually)<br>• Vesicant (rarely)  | Cold<br>Apply cold pack for 15–20 minutes at least 4 times a day for the first 24 hours.                                                   | The drug has been associated with irritation, swelling, pain, and tissue damage, which may be severe.<br>Assess the infiltration area for pain, blister formation, and skin sloughing as needed or per institutional policy.<br>Instruct patients to monitor the infiltration site and report fever, chills, blistering, skin sloughing, and worsening pain.<br>(ADC Therapeutics America, 2021)                                                                                                                                                                                                                                                                                                                                       |
| Melphalan (Alkeran®, Evomela®, Pepaxto®)<br>• Irritant (usually)<br>• Vesicant (rarely) | Cold<br>Apply cold pack for 15–20 minutes at least 4 times a day for the first 24 hours.                                                   | Assess the infiltration area for pain, blister formation, and skin sloughing as needed or per institutional policy.<br>Instruct patients to monitor the infiltration site and report fever, chills, blistering, skin sloughing, and worsening pain.<br>(Acrotech Biopharma, 2019; Ener et al., 2004; Goolsby & Lombardo, 2006; GlaxoSmithKline, 2011; Oncoceptides, 2021; Sauerland et al., 2006)                                                                                                                                                                                                                                                                                                                                      |
| Oxaliplatin (Eloxatin®)<br>• Irritant (usually)<br>• Vesicant (rarely)                  | Heat<br>Apply warm pack for 15–20 minutes at least 4 times a day for the first 24–48 hours.                                                | A warm pack may reduce local pain and inflammation. Ice packs should be avoided as they may exacerbate acute neurologic symptoms.<br>Elevate extremity (peripheral extravasations).<br>High-dose dexamethasone (8 mg twice daily for up to 14 days) has been reported to reduce oxaliplatin infiltration-related inflammation.<br>Assess the infiltration area for pain, blister formation, and skin sloughing as needed or per institutional policy.<br>Instruct patients to monitor the infiltration site and report fever, chills, blistering, skin sloughing, and worsening pain.<br>(Azaïs et al., 2015; de Lemos & Walisser, 2005; Foo et al., 2003; Kennedy et al., 2003; Kretzschmar et al., 2003; Sanofi-Aventis U.S., 2020a) |
| Streptozocin (Zanosar®)<br>• Irritant (usually)<br>• Vesicant (rarely)                  | Cold<br>Apply cold pack for 15–20 minutes at least 4 times a day for the first 24 hours.                                                   | Assess the infiltration area for pain, blister formation, and skin sloughing as needed or per institutional policy.<br>Instruct patients to monitor the infiltration site and report fever, chills, blistering, skin sloughing, and worsening pain.<br>Instruct patients with peripheral extravasations to report arm or hand swelling and stiffness.<br>(Teva Pharmaceuticals, 2021)                                                                                                                                                                                                                                                                                                                                                  |
| Topotecan (Hycamtin®)<br>• Irritant (usually)                                           | Cold<br>Apply cold pack for 15–20 minutes at least 4 times a day for the first 24 hours.                                                   | Assess the infiltration area for pain, blister formation, and skin sloughing as needed or per institutional policy.<br>Instruct patients to monitor the infiltration site and report fever, chills, blistering, skin sloughing, and worsening pain.<br>(Novartis Pharmaceuticals, 2019)                                                                                                                                                                                                                                                                                                                                                                                                                                                |

- e) Enfortumab vedotin-ejfv: In one study of 310 patients receiving enfortumab vedotin-ejfv, 1.3% experienced skin and soft tissue reactions, including delayed onset of secondary cellulitis, bullae, or exfoliation (Astellas Pharma US, 2021; Rosenberg et al., 2019).
- f) 5-Fluorouracil: The drug is administered through a central venous line using an infusion pump for continuous IV infusion regimens (Spectrum Pharmaceuticals, 2016).
- g) Irinotecan: Care should be taken to avoid the extravasation of irinotecan. If infiltration occurs, topical flushing of the skin with sterile water and application of ice is recommended (Pfizer, 2020).
- h) Loncastuximab tesirine-lpyl: Extravasation has been associated with irritation, swelling, pain, and potentially severe tissue damage. The infusion site should be monitored for possible subcutaneous infiltration during drug administration (ADC Therapeutics America, 2021).
- i) Melphalan (Alkeran®, Evomela®) and melphalan flufenamide (Pepaxto®)
  - (1) These drugs have been classified differently depending on the reference, as neither an irritant nor a vesicant (Dorr et al., 1986), as an irritant (Ener et al., 2004; Goolsby & Lombardo, 2006), and as a vesicant (Sauerland et al., 2006). Infiltration may cause local tissue damage (Acrotech Biopharma, 2019; GlaxoSmithKline, 2011; Oncopeptides, 2021).
  - (2) Care should be taken to avoid possible infiltration (e.g., monitor the IV site during a melphalan [Alkeran] infusion). With poor peripheral venous access, a central venous line is recommended. Alkeran should be administered through a fast-running IV solution into an injection port on the IV tubing; it should not be administered by direct injection into a peripheral vein (GlaxoSmithKline, 2011).
  - (3) Melphalan (Evomela) and melphalan flufenamide (prodrug of melphalan; Pepaxto) require a central line for administration (Acrotech Biopharma, 2019; Oncopeptides, 2021).
- j) Oxaliplatin
  - (1) The drug has been described as both an irritant and a vesicant (Azaïs et al., 2015; de Lemos & Walisser, 2005; Kennedy et al., 2003). Case reports describe induration, edema, red-brown skin discoloration, hyperpigmentation, and rare instances of tissue necrosis (Azaïs et al., 2015).
  - (2) Infiltration has included necrosis and injection site reactions, such as redness, swelling, and pain (Sanofi-Aventis U.S., 2020a).
  - (3) Kretzschmar et al. (2003) retrospectively reviewed 11 cases of peripheral oxaliplatin infiltration and found that even with large-volume (40 mg or greater) extravasations of oxaliplatin, tissue necrosis did not occur.
  - (4) Pericay et al. (2009) published a case report of a 165 mg dose of oxaliplatin that infiltrated when a noncoring needle dislodged from an implanted port, resulting in edema and skin discoloration. They concluded that the effect was of an irritant rather than a vesicant.
  - (5) In a case report, inadvertent intrathoracic infiltration of oxaliplatin caused pleural effusion and mediastinitis. Shortness of breath and chest pain resolved within a week of discontinuing the oxaliplatin infusion and initiating IV antibiotics (Leon-Ferre et al., 2012).
  - (6) Because cold packs cause local vasoconstriction, they may precipitate or worsen the cold neuropathy associated with oxaliplatin (Foo et al., 2003; Sanofi-Aventis U.S., 2020a).
  - (7) A warm pack applied to an oxaliplatin infiltration site is preferable and may reduce local pain and inflammation (Foo et al., 2003; Sanofi-Aventis U.S., 2020a).
  - (8) High-dose dexamethasone (8 mg twice daily for up to 14 days) has been reported to reduce oxaliplatin infiltration-related inflammation (Kretzschmar et al., 2003).
- k) Ado-trastuzumab emtansine
  - (1) Two case studies of ado-trastuzumab emtansine extravasation noted erythema, pain, blisters, and hyperpigmentation without full-thickness necrosis (Sallevelt et al., 2020; Shafae et al., 2017).
  - (2) The infusion site should be closely monitored for possible subcutaneous infiltration during drug administration (Genentech, 2020a).
- l) Vinorelbine
  - (1) This drug has been described as an irritant (de Lemos, 2005) and a vesicant (Ener et al., 2004; Goolsby & Lombardo, 2006; Hadaway, 2007; Sauerland et al., 2006). Case reports have described skin discoloration, chemical phlebitis, localized



rash, urticaria, blistering, and rarely, skin sloughing (Manganoni et al., 2012).

- (2) Extravasation can result in severe tissue injury, local tissue necrosis, and thrombophlebitis. Immediately stop the drug and institute recommended management procedures. Extravasation may cause local tissue necrosis or thrombophlebitis (Pierre Fabre Pharmaceuticals, 2020).
  - (3) A case report of vinorelbine infiltration from an implanted port described erythema and blister formation followed by ulceration, which was treated with heat, antibiotics, and subcutaneous hyaluronidase (Das & Gogia, 2016).
  - (4) Rapid IV infusion over 6–10 minutes followed by a flush of more than 75–125 ml of IV fluid may reduce vinorelbine-induced venous irritation (de Lemos, 2005).
3. Risk factors for irritation
    - a) Small veins
    - b) Prior treatment with irritating or sclerosing drugs, such as chemotherapy
  4. Possible etiologies of venous irritation (Gorski et al., 2021)
    - a) Low or high pH (less than 5 or greater than 9) of infused drugs
    - b) Solutions with high osmolality
    - c) Concentrated drugs or infusion solutions
  5. Signs and symptoms of venous irritation (see Table 13-1)
  6. Management of venous irritation
    - a) Application of a warm pack may reduce local discomfort.
    - b) Restarting the peripheral IV in a larger vein in another location may be indicated.
    - c) Consult a pharmacist to explore further dilution of irritating medications.
    - d) Instruct patients to report the development of a hard cord along the vein, pain, erythema, and temperature elevation.

#### D. Flare reaction

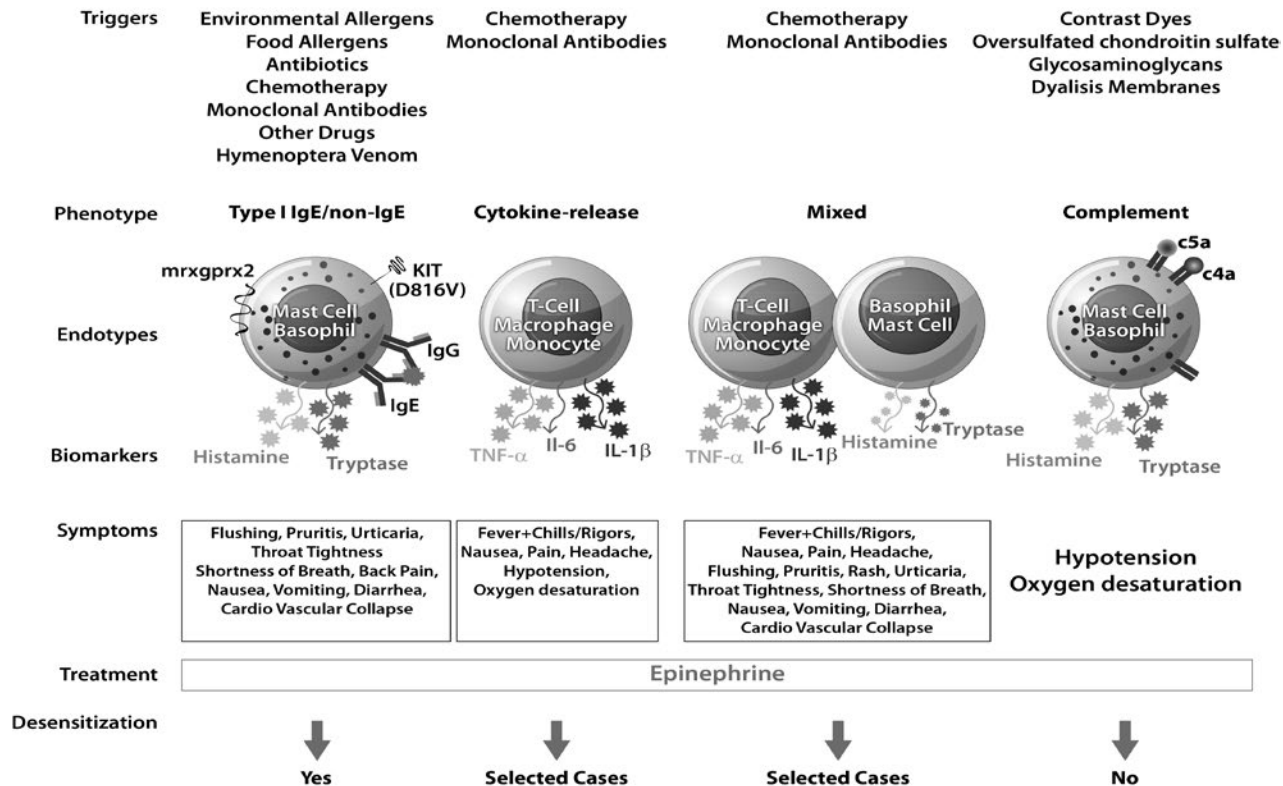
1. Flare reaction is characterized by transient erythema along the vein above the peripheral IV site and may be accompanied by pruritus and urticaria; blood return is present (Kreidieh et al., 2016; Wickham et al., 2006; see Appendix I).
2. Reaction may be observed during peripheral administration of anthracyclines (Kreidieh et al., 2016; Wickham et al., 2006).
3. It may occur during peripheral administration of doxorubicin and is thought to be caused by the local

release of histamine from mast cells or basophils (Curran et al., 1990).

4. Management of flare reaction (Gill et al., 2018)
  - a) Verify the presence of blood return. If absent, assess for signs and symptoms of extravasation.
  - b) Flush the vein slowly with saline and observe for resolution of flare, usually within 45 minutes.
  - c) An antihistamine may be used to treat a flare reaction and for premedication with subsequent cycles (Wilkes & Barton-Burke, 2020).
  - d) If resolution does not occur, contact the provider.
  - e) Do not resume the infusion through the IV site until the flare reaction resolves completely and a brisk blood return has been confirmed. Consider restarting the IV in another site.
  - f) Document the flare reaction, including treatment and the patient response.

#### E. Acute infusion-related reactions

1. Many systemic infusional cancer treatments, including chemotherapy and monoclonal antibodies, pose a risk for mild, moderate, and severe reactions, which can interrupt an optimal treatment plan in the short or long term. Optimal cancer treatment depends on patients receiving a full course of first-line therapy to achieve the best response (Castells et al., 2022). Oncology nurses need to be well informed and competent about the risk for reactions, short- and long-term management of reactions, ability to perform critical assessments, documentation, and collaboration with the treatment team to facilitate patient-centered care planning that leads to optimal outcomes.
  - a) Understanding the pathophysiology of acute infusion-related reactions using a precision medicine framework is helpful to clinicians when planning interventions (Jimenez-Rodriguez et al., 2018).
  - b) Using the precision medicine framework, acute infusion-related reactions are broadly described by their phenotype as standard infusion reactions (SIRs) attributed to an irritant effect, a type 1 hypersensitivity reaction (HSR) immunoglobulin E (IgE) or non-IgE mediated, a cytokine release reaction/syndrome (CRR/CRS), or a mixed HSR/CRR/CRS reaction (see Figure 13-2). This framework links the clinical presentation (phenotype) to the cellular and molecular mechanisms (endotypes) of the reaction. The phenotype and endotype are then linked to the symptoms and diagnostic biomarkers (e.g., skin testing, tryptase, IgE, interleukin-6) to better diagnose, treat, and ultimately prevent these acute

**FIGURE 13-2.** Pathways of Anaphylaxis

IgE—immunoglobulin E; IgG—immunoglobulin G; IL—interleukin; TNF- $\alpha$ —tumor necrosis factor alpha

Note. From "Diagnosis and Management of Anaphylaxis in Medicine," by M. Castells, 2017, *Journal of Allergy and Clinical Immunology*, 140(2), p. 323 (<https://doi.org/10.1016/j.jaci.2017.06.012>). Copyright 2017 by American Academy of Allergy, Asthma, and Immunology. Reprinted with permission.

infusion-related reactions. Using this precision medicine framework, clinicians can better contribute to establishing a collaborative and standardized plan of care for patients at risk of and experiencing an acute infusion-related reaction (Jakubovic et al., 2020; Jimenez-Rodriguez et al., 2018; Tsao et al., 2021).

c) A SIR phenotype can occur with any medication administered intravenously.

- (1) In general, allergists describe SIRs as mild, reversible, and may represent an irritant effect of the causative agent. Some may be severe, making it prudent to differentiate between SIR, type 1 HSR, CRR/CRS, or mixed HSR/CRR/CRS reaction, as the latter three are often characterized by an allergic component that could lead to anaphylaxis (Castells et al., 2022).
- (2) SIRs involving monoclonal antibodies may result from the antibody–antigen interactions that release cytokines; however, the exact mechanism is unclear.

Reactions with monoclonal antibodies may be mild and usually occur with the first dose.

- (3) Although SIRs can affect any organ system in the body, the most common signs and symptoms are fever and shaking chills, flushing and itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, back or abdominal pain, nausea, vomiting and diarrhea, and various types of skin rashes (LaCasce et al. 2021).
  - (4) Reactions with immunotherapy agents, such as rituximab, trastuzumab, and cetuximab, are mostly SIRs in nature and may also potentially induce anaphylaxis (LaCasce et al., 2021; see Table 13-5).
- d) A type 1 HSR phenotype is unexpected, mediated by the immune system (IgE), and is usually allergic.
- (1) It can be mild or moderate or can lead to a severe anaphylactic reaction.



**TABLE 13-5.** Immunotherapy Drugs and Associated Acute Infusion-Related Reactions

| Drug                                              | Reaction Symptoms                                                                                                                                          | Frequency                                                                                                                                                                      | Management                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Prevention                                                                                                                                                                                                                                                                                                                                 |
|---------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ado-trastuzumab emtansine (Kadcyla <sup>®</sup> ) | Flushing, chills, fever, dyspnea, hypotension, wheezing, bronchospasm, tachycardia                                                                         | Uncommon<br>Majority are grade 1–2.                                                                                                                                            | <p>Infusion-related reaction</p> <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat symptoms with supportive care medications.</li> <li>• After resolution of symptoms, consider restarting.</li> </ul> <p>Anaphylaxis</p> <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat for anaphylaxis.</li> <li>• Do not rechallenge.</li> <li>• Permanently discontinue use unless referred to an allergist.</li> </ul>                                           | Premedications: routine pre-medication not indicated (Cáceres et al., 2019; Genentech, 2020; LaCasce et al., 2021; Wilkes & Barton-Burke, 2020)                                                                                                                                                                                            |
| Alemtuzumab (Campath <sup>®</sup> )               | Rigors, fever, rash, nausea, vomiting, dyspnea, hypotension, fatigue, urticaria, pruritus, headache, hives, chest discomfort, tachycardia, dizziness, pain | <p>Common: IV route</p> <p>Uncommon: SC route provides a milder systemic reaction. Local site reactions are common.</p> <p>Symptoms decline with continued administration.</p> | <p>Infusion-related reaction</p> <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat symptoms with supportive care medications.</li> <li>• Add additional corticosteroid.</li> <li>• After resolution of symptoms, consider restarting.</li> </ul> <p>Anaphylaxis</p> <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat for anaphylaxis.</li> <li>• Do not rechallenge.</li> <li>• Permanently discontinue use unless referred to an allergist.</li> </ul> | <p>Premedications: antipyretic, H<sub>1</sub> blocker</p> <p>Gradual dose escalation to the recommended maintenance dose over 3–7 days is required at initiation and after any break in therapy &gt; 7 days.</p> <p>(Cáceres et al., 2019; LaCasce et al., 2021; Millennium &amp; ILEX Partner, 2001; Wilkes &amp; Barton-Burke, 2020)</p> |
| Atezolizumab (Tecentriq <sup>®</sup> )            | Fever, chills, headache, nausea<br>Severe: throat tightness, shortness of breath, desaturation                                                             | Uncommon<br>Grade 3 frequency is < 2%.                                                                                                                                         | <p>Infusion-related reaction</p> <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat symptoms with supportive care medications.</li> <li>• Add additional corticosteroid.</li> <li>• After resolution of symptoms, consider restarting.</li> </ul> <p>Anaphylaxis</p> <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat for anaphylaxis.</li> <li>• Do not rechallenge.</li> <li>• Permanently discontinue use unless referred to an allergist.</li> </ul> | <p>Premedications: routine pre-medication not indicated</p> <p>For grade 1–2 reactions, consider using premedications with subsequent doses.</p> <p>(Cáceres et al., 2019; Genentech, 2018; LaCasce et al., 2021; Wilkes &amp; Barton-Burke, 2020)</p>                                                                                     |
| Avelumab (Bavencio <sup>®</sup> )                 | Fever, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, urticaria                                                              | <p>Common</p> <p>Grade 1–2 frequency is 25%.</p> <p>Grade 3 frequency is &lt; 1%.</p>                                                                                          | <p>Infusion-related reaction</p> <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat symptoms with supportive care medications.</li> <li>• Add additional corticosteroid.</li> <li>• After resolution of symptoms, consider restarting.</li> </ul> <p>Anaphylaxis</p> <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat for anaphylaxis.</li> <li>• Do not rechallenge.</li> <li>• Permanently discontinue use unless referred to an allergist.</li> </ul> | <p>Premedications: antipyretic, H<sub>1</sub> blocker</p> <p>Administer prior to the first 4 infusions and subsequently as needed.</p> <p>(Cáceres et al., 2019; EMD Serono, 2019; LaCasce et al., 2021; Wilkes &amp; Barton-Burke, 2020)</p>                                                                                              |

(Continued on next page)

**TABLE 13-5.** Immunotherapy Drugs and Associated Acute Infusion-Related Reactions (*Continued*)

| Drug                      | Reaction Symptoms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Frequency                                                                         | Management                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Prevention                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|---------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Bevacizumab (Avastin®)    | Dyspnea, flushing, redness, rash, wheezing, hypotension, hypertension, oxygen desaturation, chest pain, headache, rigors, nausea, vomiting                                                                                                                                                                                                                                                                                                                                                                                                                  | Uncommon<br>Grade 1–2 frequency is < 3%.<br>Grade 3 frequency is 0.2%.            | Infusion-related reaction <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat symptoms with supportive care medications.</li> <li>• Add additional corticosteroid.</li> <li>• After resolution of symptoms, consider restarting.</li> </ul> Anaphylaxis <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat for anaphylaxis.</li> <li>• Do not rechallenge.</li> <li>• Permanently discontinue use unless referred to an allergist.</li> </ul> | Premedications: routine premedication not indicated<br>A rapid infusion rate does not appear to increase the incidence of reactions.<br>The standard administration schedule includes the following: <ul style="list-style-type: none"> <li>• First dose: 90 minutes 1st dose</li> <li>• Second dose: 60 minutes</li> <li>• Subsequent doses: 30 minutes</li> </ul> (Cáceres et al., 2019; Genentech, 2009; LaCasce et al., 2021; Wilkes & Barton-Burke, 2020) |
| Blinatumomab (Blinicyto®) | Infusion-related reactions: fever, hypotension, myalgia, acute kidney injury, hypertension, erythematous rash<br>Infusion-related reactions may be clinically indistinguishable from cytokine release syndrome reactions: fever, headache, nausea, asthenia, hypotension, elevations in serum aminotransferases and bilirubin, disseminated intravascular coagulation, capillary leak syndrome, hemophagocytic histiocytosis/macrophage activation syndrome.<br>Seizures, encephalopathy, tremor, dizziness, aphasia, and confusion may be found with both. | Common: 11%<br>Reactions are typically associated with the first week of a cycle. | Infusion-related reaction <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat symptoms with supportive care medications.</li> <li>• Add additional corticosteroid.</li> <li>• After resolution of symptoms, consider restarting.</li> </ul> Anaphylaxis <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat for anaphylaxis.</li> <li>• Do not rechallenge.</li> <li>• Permanently discontinue use unless referred to an allergist.</li> </ul> | Premedications: antipyretic; glucocorticoid prior to the first dose of each cycle, prior to each intracycle dose increase, or when restarting after an interruption of 4 or more hours<br>Consider hospitalization for the first 3–9 days of the first cycle and the first 2 days of the second cycle due to the risk of cytokine release syndrome.<br>(Amgen, 2017; Cáceres et al., 2019; LaCasce et al., 2021; Wilkes & Barton-Burke, 2020)                  |
| Brentuximab (Adcetris®)   | Rash, shortness of breath, breathless sensation, chest tightness, fever, back pain                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Common: 13%<br>Grade 3 frequency is 10%.<br>Anaphylaxis is rare.                  | Infusion-related reaction <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat symptoms with supportive care medications.</li> <li>• Add additional corticosteroid.</li> <li>• After resolution of symptoms, consider restarting.</li> </ul> Anaphylaxis <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat for anaphylaxis.</li> <li>• Do not rechallenge.</li> <li>• Permanently discontinue use unless referred to an allergist.</li> </ul> | Premedications: routine premedication not indicated<br>Premedications if prior reaction: antipyretic, glucocorticoid, H <sub>1</sub> blocker<br>(Cáceres et al., 2019; LaCasce et al., 2021; Seattle Genetics, 2014; Wilkes & Barton-Burke, 2020)                                                                                                                                                                                                              |

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**TABLE 13-5.** Immunotherapy Drugs and Associated Acute Infusion-Related Reactions (*Continued*)

| Drug                    | Reaction Symptoms                                                                                                                                                                                                                                                                                        | Frequency                                                                                                                                                                                                            | Management                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Prevention                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|-------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cemiplimab (Libtayo®)   | Fever, chills, headache, nausea<br>Severe: throat tightness, shortness of breath, desaturation                                                                                                                                                                                                           | Uncommon<br>Grade 3 frequency is 0.2%.                                                                                                                                                                               | Infusion-related reaction <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat symptoms with supportive care medications.</li> <li>• Add additional corticosteroid.</li> <li>• After resolution of symptoms, consider restarting.</li> </ul> Anaphylaxis <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat for anaphylaxis.</li> <li>• Do not rechallenge.</li> <li>• Permanently discontinue use unless referred to an allergist.</li> </ul>                                                     | Premedications: routine premedication not indicated (Cáceres et al., 2019; LaCasce et al., 2021; Regeneron Pharmaceuticals, 2018; Wilkes & Barton-Burke, 2020)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Cetuximab (Erbix®)      | Bronchospasm, stridor, hoarseness, urticaria, nausea and vomiting, hypotension, hypertension, loss of consciousness, shock<br>Fatal reactions are seen with squamous cell carcinoma of the head and neck, with concurrent radiation therapy, or if given with platinum-based therapy and 5-fluorouracil. | Common<br>Grade 1–2 frequency is 25%.<br>Grade 3 frequency is 3%–4%.<br>More than 90% of reactions occur during the first exposure.<br>A history of asthma or drug reaction increases the risk of a severe reaction. | Infusion-related reaction <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat symptoms with supportive care medications.</li> <li>• After resolution of symptoms, rechallenge at a slower rate.</li> <li>• Give additional H<sub>1</sub> blocker.</li> <li>• Monitor for 60 minutes.</li> </ul> Anaphylaxis <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat for anaphylaxis.</li> <li>• Do not rechallenge.</li> <li>• Permanently discontinue use unless referred to an allergist.</li> </ul> | Premedications: antipyretic, glucocorticoid, H <sub>1</sub> blocker (as cetuximab is typically given with irinotecan)<br>If given alone: glucocorticoid, H <sub>1</sub> blocker<br>If no reaction after the first dose, an H <sub>1</sub> blocker is optional.<br>Consider 60 minutes of observation following each administration with the previous reaction.<br>Skin testing has not been demonstrated to be effective.<br>Begin infusion at a slower rate and increase the rate to administer the remainder over 90 minutes without infusion-related reaction in the initial 30 minutes.<br>(Cáceres et al., 2019; ImClone, 2021; LaCasce et al., 2021; Wilkes & Barton-Burke, 2020) |
| Daratumumab (Darzalex®) | Nasal congestion, rhinitis, cough, chills, throat irritation, vomiting, nausea, hypertension, bronchospasm, hypoxia, dyspnea, laryngeal edema, pulmonary edema, hypertension, hypotension, headache, rash, urticaria, pruritus                                                                           | Common: 50%<br>Majority are grade 1–2 and occur during the first infusion.<br>Reactions have occurred up to 48 hours after infusion.                                                                                 | Infusion-related reaction <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat symptoms with supportive care medications.</li> <li>• Add additional corticosteroid.</li> <li>• After resolution of symptoms, consider restarting.</li> </ul> Anaphylaxis <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat for anaphylaxis.</li> <li>• Do not rechallenge.</li> <li>• Permanently discontinue use unless referred to an allergist.</li> </ul>                                                     | Premedications: antipyretic, glucocorticoid, H <sub>1</sub> blocker<br>Begin infusion at a slower initial rate and increase in the absence of infusion-related reaction.<br>A 4-hour observation period is required on cycle 1, day 1 for patients who experience a reaction with previous administration (regardless if IV or SC route) and patients who have not received daratumumab in the past 6 months.                                                                                                                                                                                                                                                                           |

(Continued on next page)

**TABLE 13-5.** Immunotherapy Drugs and Associated Acute Infusion-Related Reactions (*Continued*)

| Drug                                             | Reaction Symptoms                                                                                                                                                                                                | Frequency                                                                                                                  | Management                                                                                                                                                                                                                                                                                                                                                                                                                                    | Prevention                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|--------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Daratumumab<br>(Darzalex®)<br>( <i>Cont.</i> )   |                                                                                                                                                                                                                  |                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                               | <p>Premedications if prior reaction:</p> <ul style="list-style-type: none"> <li>Consider long-acting bronchodilators or inhaled glucocorticoids, and discontinue if there is no major infusion reaction after 4 doses.</li> <li>Use glucocorticoid on the first and second day, and discontinue if there is no major infusion reaction after 4 doses.</li> <li>Consider a split dose for the first dose, where the initial dose is divided into 2 doses, each administered with the same premedications once daily over 2 consecutive days.</li> </ul> <p>Premedications (SC dose): antipyretic, glucocorticoid, H<sub>1</sub> blocker</p> <p>When converting patients currently on IV to SC, 4-hour monitoring is not required unless patients have reacted to a previous dose.</p> <p>(Cáceres et al., 2019; Janssen Biotech, 2016; LaCasce et al., 2021; Wilkes &amp; Barton-Burke, 2020)</p> |
| Daratumumab and hyaluronidase (Darzalex Faspro®) | Nasal congestion, rhinitis, cough, chills, throat irritation, vomiting, nausea, hypertension, bronchospasm, hypoxia, dyspnea, laryngeal edema, pulmonary edema, hypotension, headache, rash, urticaria, pruritus | SC dose has less risk for an infusion-related reaction than IV dose (13% vs. 34%); however, reaction symptoms are similar. | <ul style="list-style-type: none"> <li>Stop drug.</li> <li>Treat symptoms with supportive care medications.</li> <li>Add additional corticosteroid.</li> <li>After resolution of symptoms, consider restarting.</li> </ul> <p>Anaphylaxis</p> <ul style="list-style-type: none"> <li>Stop drug.</li> <li>Treat for anaphylaxis.</li> <li>Do not rechallenge.</li> <li>Permanently discontinue use unless referred to an allergist.</li> </ul> | <p>Premedications (SC dose): antipyretic, glucocorticoid, H<sub>1</sub> blocker</p> <p>A 3.5-hour observation required on cycle 1, day 1 for patients who experience a reaction with previous administration (regardless if IV or SC route) and patients who have not received daratumumab in the past 6 months</p> <p>Premedications if prior reaction</p> <ul style="list-style-type: none"> <li>Consider long-acting bronchodilators or inhaled glucocorticoids, and discontinue if there is no major infusion reaction after 4 doses.</li> <li>Use glucocorticoid on the first and second day, and discontinue if there is no major infusion reaction after 4 doses.</li> </ul> <p>(Cáceres et al., 2019; Janssen Biotech, 2021; LaCasce et al., 2021; Wilkes &amp; Barton-Burke, 2020)</p>                                                                                                  |

(Continued on next page)

**TABLE 13-5.** Immunotherapy Drugs and Associated Acute Infusion-Related Reactions (*Continued*)

| Drug                                 | Reaction Symptoms                                                                            | Frequency                                                                                                                                   | Management                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Prevention                                                                                                                                                                                                                                                                                                                                |
|--------------------------------------|----------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Dinutuximab (Unituxin <sup>®</sup> ) | Fever, hypotension, urticaria, bronchospasm, facial and upper airway edema, dyspnea, stridor | Common<br>Hypersensitivity reaction and cytokine release syndrome (26%)<br>Infusion-related reactions are seen up to 24 hours postinfusion. | Infusion-related reaction <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat symptoms with supportive care medications.</li> <li>• Grade 1–2 reactions respond to antipyretic and antihistamine.</li> <li>• After resolution of symptoms, rechallenge at slower infusion rate with close monitoring.</li> </ul> Anaphylaxis <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat for anaphylaxis. Do not rechallenge.</li> <li>• Permanently discontinue use unless referred to an allergist.</li> </ul> | Premedications: antipyretic, glucocorticoid, H <sub>1</sub> blocker<br>It is recommended to repeat the administration of H <sub>1</sub> blocker every 4–6 hours as needed.<br>Postinfusion observation of 4 hours is recommended.<br>(Cáceres et al., 2019; LaCasce et al., 2021; United Therapeutics, 2015; Wilkes & Barton-Burke, 2020) |
| Durvalumab (Imfinzi <sup>®</sup> )   | Fever, chills, headache, nausea                                                              | Uncommon: < 2%<br>Majority are grade 1–2.                                                                                                   | Infusion-related reaction <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat symptoms with supportive care medications.</li> <li>• After resolution of symptoms, rechallenge at slower infusion rate.</li> </ul> Anaphylaxis <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat for anaphylaxis.</li> <li>• Do not rechallenge.</li> <li>• Permanently discontinue use unless referred to an allergist.</li> </ul>                                                                                     | Premedications: routine premedication not indicated<br>(AstraZeneca Pharmaceuticals, 2020; Cáceres et al., 2019; LaCasce et al., 2021; Wilkes & Barton-Burke, 2020)                                                                                                                                                                       |
| Elotuzumab (Empliciti <sup>®</sup> ) | Fever, chills, hypertension, bradycardia, hypotension                                        | Uncommon: 10%, of which 70% occurred with the first dose<br>Majority are grade 1–2.<br>Grade 3 frequency is 1%.                             | Infusion-related reaction <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat symptoms with supportive care medications.</li> <li>• After resolution of symptoms, consider restarting.</li> </ul> Anaphylaxis <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat for anaphylaxis.</li> <li>• Do not rechallenge.</li> <li>• Permanently discontinue use unless referred to an allergist.</li> </ul>                                                                                                     | Premedications: antipyretic, glucocorticoid, H <sub>1</sub> and H <sub>2</sub> blocker<br>(Bristol-Myers Squibb, 2015)                                                                                                                                                                                                                    |
| Gemtuzumab (Mylotarg <sup>®</sup> )  | Fever, chills, hypotension, tachycardia, hypoxia, respiratory failure                        | Common                                                                                                                                      | Infusion-related reaction <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat symptoms with supportive care medications.</li> <li>• After resolution of symptoms, consider restarting.</li> <li>• Monitor for 60 minutes.</li> </ul> Anaphylaxis <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat for anaphylaxis.</li> <li>• Do not rechallenge.</li> <li>• Permanently discontinue use unless referred to an allergist.</li> </ul>                                                                  | Premedications: antipyretic, glucocorticoid, H <sub>1</sub> blocker<br>(Cáceres et al., 2019; LaCasce et al., 2021; Wilkes & Barton-Burke, 2020; Wyeth Pharmaceuticals, 2017b)                                                                                                                                                            |

(Continued on next page)

**TABLE 13-5.** Immunotherapy Drugs and Associated Acute Infusion-Related Reactions (*Continued*)

| Drug                                                         | Reaction Symptoms                                                                                                                                                                                                      | Frequency                                                                                                                                                                                                                         | Management                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Prevention                                                                                                                                                                                                                                                                                                                                                                             |
|--------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <sup>90</sup> Y Ibritumomab tiuxetan (Zevalin <sup>®</sup> ) | Potentially fatal infusion reactions with features of anaphylaxis (e.g., angioedema, urticaria, bronchospasm, hypotension, hypoxia, myocardial infarction, acute respiratory distress syndrome, pulmonary infiltrates) | Uncommon<br>See rituximab package insert. Rituximab alone or as a component of the Zevalin regimen can cause severe infusion-related reactions.<br>Most reactions occur during or within 30–120 minutes after the first infusion. | Infusion-related reaction <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat symptoms with supportive care medications.</li> <li>• After resolution of symptoms, consider restarting.</li> </ul> Anaphylaxis <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat for anaphylaxis.</li> <li>• Do not rechallenge.</li> <li>• Permanently discontinue use unless referred to an allergist.</li> </ul>                                                                                                                | Premedications: antipyretic, H <sub>1</sub> blocker before the first and second infusions. Consider an H <sub>2</sub> blocker.<br>Known hypersensitivity or anaphylactic reactions to yttrium chloride, murine proteins, or rituximab are contraindications to treatment.<br>(Cáceres et al., 2019; LaCasce et al., 2021; Spectrum Pharmaceuticals, 2009; Wilkes & Barton-Burke, 2020) |
| Inotuzumab ozogamicin (Besponsa <sup>®</sup> )               | Dyspnea, fever, chills, cough, hypotension, hypertension, hot flashes, nausea                                                                                                                                          | Uncommon: 2%<br>Majority are grade 1–2 and occur during the first infusion.                                                                                                                                                       | Infusion-related reaction <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat symptoms with supportive care medications.</li> <li>• After resolution of symptoms, consider restarting.</li> <li>• Monitor for 1 hour after infusion-related reaction.</li> </ul> Anaphylaxis <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat for anaphylaxis.</li> <li>• Do not rechallenge.</li> <li>• Permanently discontinue use unless referred to an allergist.</li> </ul>                                                 | Premedications: antipyretic, glucocorticoid, H <sub>1</sub> blocker<br>(Cáceres et al., 2019; LaCasce et al., 2021; Wilkes & Barton-Burke, 2020; Wyeth Pharmaceuticals, 2017a)                                                                                                                                                                                                         |
| Isatuximab (Sarclisa <sup>®</sup> )                          | Dyspnea, cough, chills, nausea, nasal congestion, hypertension<br>Anaphylaxis has occurred.                                                                                                                            | Common: 38%<br>Majority are grade 1–2 and occur during the first infusion.<br>Grade 3 frequency is < 1%.                                                                                                                          | Infusion-related reaction <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat symptoms with supportive care medications.</li> <li>• After resolution of symptoms, restart at half the rate.</li> <li>• After 30 minutes without recurrence, the initial infusion rate can be increased incrementally.</li> </ul> Anaphylaxis <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat for anaphylaxis.</li> <li>• Do not rechallenge.</li> <li>• Permanently discontinue use unless referred to an allergist.</li> </ul> | Premedications: antipyretic, glucocorticoid, H <sub>1</sub> and H <sub>2</sub> blocker<br>Dose escalations are recommended.<br>(Cáceres et al., 2019; LaCasce et al., 2021; Sanofi-Aventis U.S., 2020b; Wilkes & Barton-Burke, 2020)                                                                                                                                                   |

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**TABLE 13-5.** Immunotherapy Drugs and Associated Acute Infusion-Related Reactions (*Continued*)

| Drug                                    | Reaction Symptoms                                                                                                                                                                                                                                                                                                                                                                   | Frequency                                                                                                                                                                                       | Management                                                                                                                                                                                                                                                                                                                                                                                                                                     | Prevention                                                                                                                                                                                                                                          |
|-----------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Mogamulizumab (Poteligeo <sup>®</sup> ) | Chills, nausea, fever, tachycardia, rigors, headache, vomiting                                                                                                                                                                                                                                                                                                                      | Common: 35%<br>Approximately 90% of reactions occur with the first infusion.<br>Approximately 42% occur without premedications compared to 32% with premedications.<br>Grade 3 frequency is 8%. | Infusion-related reaction <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat symptoms with supportive care medications.</li> <li>• After resolution of symptoms, consider restarting.</li> </ul> Anaphylaxis <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat for anaphylaxis.</li> <li>• Do not rechallenge.</li> <li>• Permanently discontinue use unless referred to an allergist.</li> </ul>         | Premedications: antipyretic, H <sub>1</sub> blocker<br>(Cáceres et al., 2019; Kyowa Kirin, 2018; LaCasce et al., 2021; Wilkes & Barton-Burke, 2020)                                                                                                 |
| Moxetumomab (Lumoxiti <sup>®</sup> )    | Chills, cough, dizziness, dyspnea, flushing, headache, hypertension, hypotension, myalgia, nausea, fever, tachycardia, vomiting, wheezing, nausea, pyrexia, chills, vomiting, headache, capillary leak syndrome                                                                                                                                                                     | Common: 50%<br>Grade 3 frequency is 11%.<br>Reactions may occur during any cycle of treatment.                                                                                                  | Infusion-related reaction <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat symptoms with supportive care medications.</li> <li>• After resolution of symptoms, consider restarting.</li> </ul> Anaphylaxis <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat for anaphylaxis.</li> <li>• Do not rechallenge.</li> <li>• Permanently discontinue use unless referred to an allergist.</li> </ul>         | Premedications: antipyretic, H <sub>1</sub> blocker<br>Premedications if prior reaction: antipyretic, H <sub>1</sub> blocker (AstraZeneca Pharmaceuticals, 2018; Cáceres et al., 2019; LaCasce et al., 2021; Wilkes & Barton-Burke, 2020)           |
| Necitumumab (Portrazza <sup>®</sup> )   | Chills, fever, dyspnea, itching, nausea, chest tightness, crampy abdominal pain, difficulty speaking, anxiety, agitation, sense of impending doom, uneasiness, desire to urinate/defecate, dizziness, flushed appearance, localized or generalized urticaria, respiratory distress with/without wheezing, hypotension, cyanosis, angioedema of face, neck, eyelids, hands, and feet | Uncommon: 1.5%<br>Majority are grade 1–2 and occur during the first infusion.<br>Grade 3 frequency is 0.4%.                                                                                     | Infusion-related reaction <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat symptoms with supportive care medications.</li> <li>• After resolution of symptoms, resume infusion rate at 50%.</li> </ul> Anaphylaxis <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat for anaphylaxis.</li> <li>• Do not rechallenge.</li> <li>• Permanently discontinue use unless referred to an allergist.</li> </ul> | Premedications: routine premedication not indicated<br>Premedications if prior reaction: antipyretic, glucocorticoid, H <sub>1</sub> blocker (Cáceres et al., 2019; Eli Lilly and Company, 2015; LaCasce et al., 2021; Wilkes & Barton-Burke, 2020) |

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**TABLE 13-5.** Immunotherapy Drugs and Associated Acute Infusion-Related Reactions (*Continued*)

| Drug                   | Reaction Symptoms                                                                                                                                                                                                                                                                                                                                                 | Frequency                                                                                                                                                                                                                                                                                                             | Management                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Prevention                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Nivolumab (Opdivo®)    | Fever, chills, headache, nausea                                                                                                                                                                                                                                                                                                                                   | Uncommon: < 1%<br>Grade 3 frequency is < 1%.                                                                                                                                                                                                                                                                          | <p>Infusion-related reaction</p> <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat symptoms with supportive care medications.</li> <li>• After resolution of symptoms, consider restarting at reduced infusion rate.</li> </ul> <p>Anaphylaxis</p> <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat for anaphylaxis.</li> <li>• Do not rechallenge.</li> <li>• Permanently discontinue use unless referred to an allergist.</li> </ul>                                                     | <p>Premedications: antipyretic, H<sub>1</sub> blocker<br/>(Bristol-Myers Squibb, 2018; Cáceres et al., 2019; LaCasce et al., 2021; Wilkes &amp; Barton-Burke, 2020)</p>                                                                                                                                                                                                                                                                                                                                                                                            |
| Obinutuzumab (Gazyva®) | <p>Nausea, fatigue, chest discomfort, hypotension, fever, vomiting, dyspnea, rash, dizziness, hypertension, chills, vomiting, headache, flushing, tachycardia, diarrhea, bronchospasm, laryngeal irritation, wheezing, laryngeal edema and auricular fibrillation</p> <p>Increased risk for severe reactions with preexisting cardiac or pulmonary conditions</p> | <p>Common<br/>65% with chronic lymphoblastic leukemia within 1,000 mg on the first infusion<br/>38% relapsed or refractory non-Hodgkin lymphoma<br/>60% untreated non-Hodgkin lymphoma</p> <p>Reactions typically occur with the first infusion but can occur with subsequent infusions and up to 24 hours later.</p> | <p>Infusion-related reaction</p> <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat symptoms with supportive care medications.</li> <li>• After resolution of symptoms, consider restarting at a reduced infusion rate.</li> </ul> <p>Anaphylaxis</p> <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat for anaphylaxis. Do not rechallenge.</li> <li>• Permanently discontinue use unless referred to an allergist.</li> </ul>                                                              | <p>Premedications (first infusion): antipyretic, glucocorticoid, H<sub>1</sub> blocker</p> <p>Premedications for subsequent infusions:</p> <ul style="list-style-type: none"> <li>• No reaction: antipyretic</li> <li>• Grade 1–2 reaction: antipyretic, H<sub>1</sub> blocker</li> <li>• Grade 3: antipyretic, glucocorticoid, H<sub>1</sub> blocker</li> </ul> <p>Stop antihypertensives 12 hours before each infusion. Dose escalations are recommended.<br/>(Cáceres et al., 2019; Genentech, 2017; LaCasce et al., 2021; Wilkes &amp; Barton-Burke, 2020)</p> |
| Ofatumumab (Arzerra®)  | Rigors, fever, fatigue, rash, increased sweating, bronchospasm, dyspnea, laryngeal and pulmonary edema, hypertension, hypotension, syncope, back pain, urticaria, angioedema                                                                                                                                                                                      | <p>Common<br/>Mild reactions occur with the first 2 weekly doses and within the first few hours.</p> <p>Reactions are less frequent and less severe during subsequent cycles.</p>                                                                                                                                     | <p>Infusion-related reaction</p> <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat symptoms with supportive care medications.</li> <li>• After resolution of symptoms for grade 1–2 reactions, resume infusion rate at 50%. For grade 3 reactions, infuse at 12 ml/hour.</li> </ul> <p>Anaphylaxis</p> <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat for anaphylaxis.</li> <li>• Do not rechallenge.</li> <li>• Permanently discontinue use unless referred to an allergist.</li> </ul> | <p>Premedications: antipyretic, glucocorticoid, H<sub>1</sub> blocker</p> <p>For doses 1, 2, and 9, with a gradual reduction in dose for infusions 3–8 and 10–12 in the absence of a ≥ grade 3 reaction during the prior infusion<br/>(Cáceres et al., 2019; Glaxo Group, 2009; LaCasce et al., 2021; Wilkes &amp; Barton-Burke, 2020)</p>                                                                                                                                                                                                                         |

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**TABLE 13-5.** Immunotherapy Drugs and Associated Acute Infusion-Related Reactions (*Continued*)

| Drug                      | Reaction Symptoms                                                                                                                          | Frequency                                                                                                    | Management                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Prevention                                                                                                                                                                                                                                               |
|---------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Olaratumab (Lartruvo®)    | Flushing, shortness of breath, bronchospasm, fever, chills<br>Severe: hypotension, anaphylactic shock, cardiac arrest                      | Common: 14%<br>Majority are grade 1–2 and occur during the first infusion (97%).<br>Grade 3 frequency is 2%. | Infusion-related reaction <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat symptoms with supportive care medications.</li> <li>• After resolution of symptoms, resume infusion rate at 50%.</li> </ul> Anaphylaxis <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat for anaphylaxis.</li> <li>• Do not rechallenge.</li> <li>• Permanently discontinue use unless referred to an allergist.</li> </ul>                    | Premedications (first cycle): glucocorticoid, H <sub>1</sub> blocker (Cáceres et al., 2019; Eli Lilly and Company, 2016; LaCasce et al., 2021; Wilkes & Barton-Burke, 2020)                                                                              |
| Panitumumab (Vectibix®)   | Anaphylaxis, bronchospasm, fever, chills, hypotension                                                                                      | Uncommon: 4%<br>Grade 3 frequency is 1%.                                                                     | Infusion-related reaction <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat symptoms with supportive care medications.</li> <li>• After resolution of symptoms, resume infusion rate at 50%.</li> </ul> Anaphylaxis <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat for anaphylaxis.</li> <li>• Do not rechallenge.</li> <li>• Permanently discontinue use unless referred to an allergist.</li> </ul>                    | Premedications: routine premedication not indicated (Amgen, 2009; Cáceres et al., 2019; LaCasce et al., 2021; Wilkes & Barton-Burke, 2020)                                                                                                               |
| Pembrolizumab (Keytruda®) | Fever, chills, rigors, wheezing, pruritis, flushing, rash, hypotension, hypoxemia<br>Severe: anaphylactic shock, cytokine release syndrome | Uncommon<br>Grade 3 frequency is 0.2%.                                                                       | Infusion-related reaction <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat symptoms with supportive care medications.</li> <li>• After resolution of symptoms, resume infusion rate of 50%.</li> </ul> Anaphylaxis <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat for anaphylaxis. Do not rechallenge.</li> <li>• Permanently discontinue use unless referred to an allergist.</li> </ul>                               | Premedications: routine premedication not indicated (Cáceres et al., 2019; LaCasce et al., 2021; Merck, 2021; Wilkes & Barton-Burke, 2020)                                                                                                               |
| Pertuzumab (Perjeta®)     | Fever, shivering, tiredness, headache, asthenia, chills, asthenia, fatigue, vomiting                                                       | Common<br>Grade 1–2 frequency is 13%.<br>Grade 3 frequency is < 1%.                                          | Infusion-related reaction <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat symptoms with supportive care medications.</li> <li>• After resolution of symptoms, consider restarting at a reduced infusion rate.</li> </ul> Anaphylaxis <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat for anaphylaxis.</li> <li>• Do not rechallenge.</li> <li>• Permanently discontinue use unless referred to an allergist.</li> </ul> | Premedications: routine premedication not indicated<br>Closely monitor for 60 minutes after the first infusion and for 30 minutes after subsequent infusions. (Cáceres et al., 2019; Genentech, 2012; LaCasce et al., 2021; Wilkes & Barton-Burke, 2020) |

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**TABLE 13-5.** Immunotherapy Drugs and Associated Acute Infusion-Related Reactions (*Continued*)

| Drug                                                          | Reaction Symptoms                                                                                                                                                                  | Frequency                                                                          | Management                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Prevention                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|---------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Pertuzumab, trastuzumab, hyaluronidase (Phesgo <sup>®</sup> ) | SC preparation does not appear to have a higher risk of systemic reactions compared to IV; however, injection site reaction and pain are more frequent.                            | Common: 21%<br>Grade 1–2: 7%–8%<br>Grade 3: 1%                                     | Injection-related reaction <ul style="list-style-type: none"> <li>• Slow down or pause the injection and treat symptoms with supportive medications.</li> </ul> Anaphylaxis <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat for anaphylaxis.</li> <li>• Do not rechallenge.</li> <li>• Permanently discontinue use unless referred to an allergist.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Premedications: routine pre-medication not indicated<br>Premedications if prior reaction: antipyretic, H <sub>1</sub> blocker<br>Closely monitor for 30 minutes after the initial dose and for 15 minutes following subsequent injections.<br>The drug is contraindicated in patients with known hypersensitivity to pertuzumab, trastuzumab, or hyaluronidase.<br>(Cáceres et al., 2019; Genentech, 2020b; LaCasce et al., 2021; Wilkes & Barton-Burke, 2020) |
| Polatuzumab (Polivy <sup>®</sup> )                            | Fever, chills, flushing, dyspnea, hypotension, urticaria<br>A severe reaction can occur up to 24 hours after receiving the drug.<br>See rituximab.                                 | Uncommon: 7%<br>Frequency is 67% for grade 1, 25% for grade 2, and 8% for grade 3. | Infusion-related reaction <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat symptoms with supportive care medications.</li> <li>• After resolution of symptoms, resume infusion rate of 50%.</li> <li>• In the absence of infusion-related symptoms, the infusion rate may be escalated in increments of 50 mg/hour every 30 minutes.</li> <li>• For the next cycle, infuse over 90 minutes.</li> <li>• If no infusion-related reaction occurs, subsequent infusions may be administered over 30 minutes.</li> <li>• With recurrent grade 2 wheezing or urticaria, discontinue use.</li> </ul> Anaphylaxis <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat for anaphylaxis.</li> <li>• Do not rechallenge.</li> <li>• Permanently discontinue use unless referred to an allergist.</li> </ul> | Premedications: antipyretic, H <sub>1</sub> blocker<br>(Cáceres et al., 2019; Genentech, 2019; LaCasce et al., 2021; Wilkes & Barton-Burke, 2020)                                                                                                                                                                                                                                                                                                              |
| Ramucirumab (Cyramza <sup>®</sup> )                           | Rigors, tremors, back-pain/spasms, chest pain/tightness, chills, flushing, dyspnea, wheezing, hypoxia, parosmia<br>Severe: bronchospasm, supraventricular tachycardia, hypotension | Uncommon: < 9%<br>Most reactions occur during the first or second infusion.        | Infusion-related reaction <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat symptoms with supportive care medications.</li> <li>• After resolution of symptoms, resume infusion rate of 50%.</li> </ul> Anaphylaxis <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat for anaphylaxis.</li> <li>• Do not rechallenge.</li> <li>• Permanently discontinue use unless referred to an allergist.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                        | Premedications: H <sub>1</sub> blocker<br>Premedications if prior reaction: antipyretic, glucocorticoid, H <sub>1</sub> blocker<br>(Cáceres et al., 2019; Eli Lilly and Company, 2020; LaCasce et al., 2021; Wilkes & Barton-Burke, 2020)                                                                                                                                                                                                                      |

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**TABLE 13-5.** Immunotherapy Drugs and Associated Acute Infusion-Related Reactions (*Continued*)

| Drug                   | Reaction Symptoms                                                                                                                                                                                                                                                                                              | Frequency                                                                                                                                                                                                                                                                                                                                                                                             | Management                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Prevention                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Rituximab (Rituxan®)   | Headache, itching, sore throat, chills, skin rash, nausea, hypotension, rhinitis, dyspnea, redness, rashes, urticaria, pruritus, asthenia, fever, hypertension, angioedema, bronchospasm, wheezing, anaphylaxis<br>SC: injection site reactions with erythema, pruritus, rash, induration, injection site pain | Common<br>A 50% risk of reaction is possible in the first infusion in the initial 30–120 minutes.<br>Grade 3–4 frequency is < 5%.<br>Reactions are markedly less common after the initial infusion.<br>Frequency is 45%–50% with SC. Majority are grade 1–2.<br>Priming the IV line with rituximab allows for slow, incremental exposure, resulting in decreased hypersensitivity reaction incidence. | Infusion-related reaction <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat symptoms with supportive care medications.</li> <li>• After resolution of symptoms, resume infusion rate at 50%.</li> </ul> Anaphylaxis <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat for anaphylaxis.</li> <li>• Do not rechallenge.</li> <li>• Permanently discontinue use unless referred to an allergist.</li> </ul>                                                                                                                                                                                                                                                | Premedications (during the first and second infusions): antipyretic, H <sub>1</sub> and H <sub>2</sub> blocker<br>Standard premedications can be eliminated during subsequent infusions without a reaction.<br>Consider glucocorticoid and H <sub>1</sub> and H <sub>2</sub> blockers the night before and prior to rechallenge, or consider dividing into 2 doses given on days 1 and 3 in patients with chronic lymphoblastic lymphoma.<br>SC: At least one full dose should be tolerated before SC administration.<br>IV: Start the first dose slowly and gradually increase the infusion rate. The first infusion is typically given over 4 hours. (Cáceres et al., 2019; Genentech, 2010b; LaCasce et al., 2021; Wilkes & Barton-Burke, 2020) |
| Siltuximab (Sylvant®)  | Back pain, chest pain or discomfort, nausea, vomiting, flushing, erythema, palpitations                                                                                                                                                                                                                        | Uncommon: 5%<br>Frequency is 0.8% for ≥ grade 3 reactions.                                                                                                                                                                                                                                                                                                                                            | Infusion-related reaction <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat symptoms with supportive care medications.</li> <li>• After resolution of symptoms, rechallenge at a slower rate.</li> </ul> Anaphylaxis <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat for anaphylaxis.</li> <li>• Do not rechallenge.</li> <li>• Permanently discontinue use unless referred to an allergist.</li> </ul>                                                                                                                                                                                                                                               | Premedications: routine premedication not indicated<br>Premedications if prior reaction: antipyretic, glucocorticoid, H <sub>1</sub> blocker (Cáceres et al., 2019; Janssen Biotech, 2020; LaCasce et al., 2021; Wilkes & Barton-Burke, 2020)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Tafasitamab (Monjuvi®) | Chills, flushing, dyspnea, hypertension                                                                                                                                                                                                                                                                        | Uncommon: 6%<br>Approximately 80% occur during the first 2 cycles.                                                                                                                                                                                                                                                                                                                                    | Infusion-related reaction <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat symptoms with supportive care medications.</li> <li>• After resolution of grade 2 reaction symptoms, restart at 50% of the rate the reaction occurred. If there is no further reaction, the rate can be increased every 30 minutes as tolerated, up to a max infusion rate equal to the reaction rate.</li> <li>• After resolution of grade 3 reaction symptoms, restart at 25% of the rate the reaction occurred. If no further reaction, the rate can be increased every 30 minutes as tolerated, up to a max infusion rate equal to 50% of the rate where the reaction occurred.</li> </ul> | Premedications: antipyretic, glucocorticoid, H <sub>1</sub> and H <sub>2</sub> blocker<br>Premedications are optional in the absence of a reaction during the first 3 infusions. (Cáceres et al., 2019; LaCasce et al., 2021; MorphoSys US, 2020; Wilkes & Barton-Burke, 2020)                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

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**TABLE 13-5.** Immunotherapy Drugs and Associated Acute Infusion-Related Reactions (*Continued*)

| Drug                                          | Reaction Symptoms                                                                                                                                                                                                                                                                                                                               | Frequency                                                                                                                                  | Management                                                                                                                                                                                                                                                                                                                                                                                                                   | Prevention                                                                                                                                                                                                                                                                                                                                                                                  |
|-----------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Tafasitamab<br>(Monjuvi®)<br>( <i>Cont.</i> ) |                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                            | Anaphylaxis <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat for anaphylaxis.</li> <li>• Do not rechallenge.</li> <li>• Permanently discontinue use unless referred to an allergist.</li> </ul>                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                             |
| Trastuzumab<br>(Herceptin®)                   | Fever, chills, headache, dyspnea, abdominal pain, hypotension, wheezing, dizziness, rhinitis, tachycardia, decreased oxygen saturation, respiratory distress, rash, nausea, vomiting, headache<br>Severe reactions: bronchospasm, angioedema, hypoxia, severe hypotension<br>Fever and chills generally do not recur with subsequent infusions. | Common<br>Grade 1–2 frequency is 40% with the first infusion and begins shortly after the start of infusion.<br>Grade 3 frequency is 0.3%. | Infusion-related reaction<br>Stop drug.<br>Treat symptoms with supportive care medications.<br>After resolution of symptoms, consider restarting.<br>Anaphylaxis <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat for anaphylaxis.</li> <li>• Do not rechallenge.</li> <li>• Permanently discontinue use unless referred to an allergist.</li> <li>• Desensitization protocols are available.</li> </ul> | Premedications: routine premedication not indicated<br>Premedications if prior reaction: antipyretic, H <sub>1</sub> and H <sub>2</sub> blocker<br>The first dose is generally administered over 90–120 minutes, with subsequent infusions shortened to 30–45 minutes if no reactions occur.<br>(Cáceres et al., 2019; Genentech, 2010a; LaCasce et al., 2021; Wilkes & Barton-Burke, 2020) |

IV—intravenous; SC—subcutaneous

- (2) A type 1 HSR can also be non-IgE mediated (nonimmune pathway); however, it may resemble an immune allergic reaction. The endotype for IgE-mediated and non-IgE-mediated reactions is mast cell and basophil activation, causing symptoms such as flushing, pruritus, hives, angioedema, shortness of breath, wheezing, nausea, vomiting, diarrhea, hypotension, oxygen desaturation, and cardiovascular collapse (Castells & Solensky, 2020; Jimenez-Rodriguez et al., 2018).
  - (3) Type 1 HSRs can occur within minutes after the start of an infusion to as late as six hours after its completion (Castells & Solensky, 2020; LaCasce et al., 2021). See Table 13-6 for examples of chemotherapy agents associated with acute infusion-related reactions.
- e) Anaphylaxis is a systemic response that can be life threatening.
- (1) Although uncommon with most antineoplastic agents, anaphylaxis is well established with platinum drugs, taxanes, pegylated liposomal doxorubicin, asparaginase, procarbazine, etoposide, bleomycin, cytarabine, and ixabepilone (Castells et al., 2022).
  - (2) Anaphylaxis with monoclonal antibodies has been reported with rituximab (< 5%), trastuzumab (0.3%), and cetuximab (3%–4%) (LaCasce et al., 2021). Reactions with platinum agents do not usually occur until the patient has received several doses (generally after six to seven cycles) (Castells et al., 2022).
  - (3) Common signs and symptoms of anaphylaxis caused by IV medications can vary from patient to patient.
  - (4) Because anaphylaxis is potentially life threatening, it needs to be identified immediately and treated with epinephrine, the only medication that can reverse life-threatening symptoms (see Tables 13-7 and 13-8).
  - (5) Glucocorticoids and antihistamines do not play a role in the immediate treatment of anaphylaxis (Shaker et al., 2020).

**TABLE 13-6.** Chemotherapy Drugs and Associated Acute Infusion-Related Reactions

| Drug                      | Reaction Symptoms                                                                                                                                                                                                              | Frequency                                                                                                                                                                                                                                                                                             | Management                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Prevention                                                                                                                                                                                                                                                                                                                                                           |
|---------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Bleomycin (Blenoxane®)    | Fever (50%–60%), hypotension, mental confusion, fever, chills, wheezing, anuria<br>Dyspnea, cough, and rash presenting as hypersensitivity pneumonitis                                                                         | Uncommon: 1%, usually occurs after the first or second dose<br>More common with lymphoma<br>Typically idiosyncratic in nature, not allergic                                                                                                                                                           | Infusion-related reaction <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat symptoms with supportive care medications.</li> <li>• After resolution of symptoms, consider restarting.</li> </ul> Anaphylaxis <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat for anaphylaxis.</li> <li>• Do not rechallenge.</li> <li>• Permanently discontinue use unless referred to an allergist.</li> </ul>                                                                  | Premedications: routine premedication not indicated<br>Premedications if prior reaction: antipyretic, H <sub>1</sub> blocker<br>A test dose is recommended by the manufacturer; however, most clinical settings have discontinued this practice, as results are not predictive.<br>(Bristol-Myers Squibb, 2010a; Castells et al., 2022; Wilkes & Barton-Burke, 2020) |
| Carboplatin (Paraplatin®) | Pruritus (particularly of the palms and soles), flushing, urticaria, facial swelling, rash, wheezing, bronchospasm, angioedema, chest tightness, dyspnea, abdominal cramping, hypotension, sense of impending doom, chest pain | Common: 12%<br>Incidence of infusion reactions increases with repeated carboplatin drug exposure. Often seen after cycles 6–8<br>Patient groups at higher risk for reactions to platin include individuals with relapsed disease, those with <i>BRCA1/2</i> variants, and children with brain tumors. | Infusion-related reaction <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat symptoms with supportive care medications.</li> <li>• After resolution of symptoms, consider restarting.</li> </ul> Anaphylaxis <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat for anaphylaxis.</li> <li>• Do not rechallenge.</li> <li>• Permanently discontinue use unless referred to an allergist.</li> </ul> Skin testing by allergy/immunology specialists may be indicated. | Premedications: routine premedication not indicated<br>(Castells et al., 2022; Teva Pharmaceuticals, 2011; Wilkes & Barton-Burke, 2020)                                                                                                                                                                                                                              |
| Cisplatin (Platinol®)     | Facial edema, bronchospasm, tachycardia, angioedema, wheezing, urticaria, hypotension, rash                                                                                                                                    | Uncommon: 1%–5%; however, the incidence is not well reported.<br>Incidence of infusion-related reactions increases with repeated drug exposure.<br>May occur within minutes of administration                                                                                                         | Infusion-related reaction <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat symptoms with supportive care medications.</li> <li>• After resolution of symptoms, consider restarting.</li> </ul> Anaphylaxis <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat for anaphylaxis.</li> <li>• Do not rechallenge.</li> <li>• Permanently discontinue use unless referred to an allergist.</li> </ul> Desensitization protocols are available.                         | Premedications: routine premedication not indicated<br>(Bristol-Myers Squibb, 2010b; Castells et al., 2022; Wilkes & Barton-Burke, 2020)                                                                                                                                                                                                                             |

(Continued on next page)

**TABLE 13-6.** Chemotherapy Drugs and Associated Acute Infusion-Related Reactions (*Continued*)

| Drug                              | Reaction Symptoms                                                                                                                                                         | Frequency                                                                                                                                                                                                                                 | Management                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Prevention                                                                                                                                                                                                                          |
|-----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Docetaxel (Taxotere®)             | Dyspnea, hypotension, bronchospasm, urticaria, rashes, edema                                                                                                              | Common: 30% during the first or second dose without premedications<br>Drug versus vehicle: It is uncertain whether it is the drug itself or the vehicle in which it is dissolved (poly-sorbate 80) responsible for the infusion reaction. | Infusion-related reaction <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat symptoms with supportive care medications.</li> <li>• After resolution of symptoms, consider restarting.</li> </ul> Anaphylaxis <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat for anaphylaxis. Do not rechallenge.</li> <li>• Permanently discontinue use unless referred to an allergist.</li> </ul> Skin testing by allergy/immunology specialists may be indicated.<br>Desensitization protocols are available.<br>Paclitaxel-sensitized patients can react to docetaxel. | Premedications: glucocorticoid for 3 days starting 1 day before chemotherapy<br>Substitute paclitaxel if clinically appropriate. (Castells, 2020; Castells et al., 2022; Sanofi-Aventis U.S., 2013; Wilkes & Barton-Burke, 2020)    |
| Doxorubicin HCl liposome (Doxil®) | Erythema, pruritus, rash, urticaria, flushing, dyspnea, facial swelling, headache, chills, chest or back pain, chest or throat tightness, tachycardia, hypotension, fever | Common: 9%–14%, usually with the first infusion                                                                                                                                                                                           | Infusion-related reaction <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat symptoms with supportive care medications.</li> <li>• After resolution of symptoms, consider restarting.</li> </ul> Anaphylaxis <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat for anaphylaxis.</li> <li>• Do not rechallenge.</li> <li>• Permanently discontinue use unless referred to allergy.</li> </ul> The initial infusion rate should not exceed 1 mg/min.<br>Desensitization protocols are available.                                                                | Premedications: glucocorticoid, H <sub>1</sub> blocker (Ben Venue Laboratories, 2007; Castells et al., 2022; Wilkes & Barton-Burke, 2020)                                                                                           |
| Etoposide (Etopophos®)            | Hypotension, dyspnea, bronchospasm, angioedema, chest discomfort                                                                                                          | Uncommon: 1%–3%<br>Drug versus vehicle: It is uncertain whether it is the drug itself or the vehicle in which it is dissolved (poly-sorbate 80) responsible for the infusion reaction.<br>May occur within minutes of administration      | Infusion-related reaction <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat symptoms with supportive care medications.</li> <li>• After resolution of symptoms, consider restarting.</li> </ul> Anaphylaxis <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat for anaphylaxis.</li> <li>• Do not rechallenge.</li> <li>• Permanently discontinue use unless referred to an allergist.</li> </ul>                                                                                                                                                             | Premedications: routine premedication not indicated<br>Premedications if prior reaction: glucocorticoid, H <sub>1</sub> and H <sub>2</sub> blocker (Bristol-Myers Squibb, 2017; Castells et al., 2022; Wilkes & Barton-Burke, 2020) |

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**TABLE 13-6.** Chemotherapy Drugs and Associated Acute Infusion-Related Reactions (*Continued*)

| Drug                                 | Reaction Symptoms                                                                                                                                                                                                                                                       | Frequency                                                                                                                                                                                                                                                               | Management                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Prevention                                                                                                                                                                                                                                                                                                                                                                                            |
|--------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ixabepilone (Ixempra <sup>®</sup> )  | Itching, chills, fever, dizziness, nausea, chest tightness, cramping, abdominal pain, anxiety, agitation, difficulty speaking, sense of impending doom, uneasiness, bronchospasm, angioedema, urticaria, respiratory distress, hypotension                              | Uncommon: 1%<br>Drug versus vehicle: It is uncertain whether it is the drug itself or the vehicle in which it is dissolved (Cremophor) responsible for the infusion reaction.                                                                                           | Infusion-related reaction <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat symptoms with supportive care medications.</li> <li>• After resolution of symptoms, consider restarting.</li> </ul> Anaphylaxis <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat for anaphylaxis.</li> <li>• Do not rechallenge.</li> <li>• Permanently discontinue use unless referred to an allergist.</li> </ul>                                                                                                                                 | Premedications: H <sub>1</sub> and H <sub>2</sub> blocker<br>Premedications if prior reaction: glucocorticoid, H <sub>1</sub> and H <sub>2</sub> blocker (Bristol-Myers Squibb, 2021a; Castells et al., 2022; Wilkes & Barton-Burke, 2020)                                                                                                                                                            |
| Oxaliplatin (Eloxatin <sup>®</sup> ) | Urticaria, pruritis, flushing, angioedema, chest pain, bronchospasm, dyspnea, hypotension, rash<br>Acute neuropathic pain during infusion has been reported and may be considered cytokine release reaction/cytokine release syndrome, exacerbated by exposure to cold. | Common: 0.5%–25%, most common with cycle 7–9 exposure to a platinum drug<br>Incidence of infusion-related reactions increases with repeated platinum drug exposure.                                                                                                     | Infusion-related reaction <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat symptoms with supportive care medications.</li> <li>• After resolution of symptoms, consider restarting.</li> </ul> Anaphylaxis <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat for anaphylaxis.</li> <li>• Do not rechallenge.</li> <li>• Permanently discontinue use unless referred to an allergist.</li> </ul> Desensitization protocols are available.                                                                                        | Premedications: routine premedication not indicated<br>Premedications if prior reaction: glucocorticoid, H <sub>1</sub> and H <sub>2</sub> blocker (Castells et al., 2022; Sanofi-Aventis U.S., 2020a; Wilkes & Barton-Burke, 2020)                                                                                                                                                                   |
| Paclitaxel (Taxol <sup>®</sup> )     | Urticaria, angioedema, bronchospasm, dyspnea, hypotension                                                                                                                                                                                                               | Common: Most reactions occur during the first or second infusion (30%).<br>Grade 3 frequency is 2%–4%.<br>Drug versus vehicle: It is uncertain whether it is the drug itself or the vehicle in which it is dissolved (Cremophor) responsible for the infusion reaction. | Infusion-related reaction <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat symptoms with supportive care medications.</li> <li>• After resolution of symptoms, rechallenge at a slower rate.</li> </ul> Anaphylaxis <ul style="list-style-type: none"> <li>• Stop drug.</li> <li>• Treat for anaphylaxis.</li> <li>• Do not rechallenge.</li> <li>• Permanently discontinue use unless referred to an allergist.</li> </ul> Patients with positive skin testing for paclitaxel may react to paclitaxel preparations that do not contain Cremophor. | Premedications: glucocorticoid, H <sub>1</sub> and H <sub>2</sub> blocker<br>If no hypersensitivity reaction after first and second dose, consider discontinuing glucocorticoid and H <sub>1</sub> blocker from premedications.<br>The provider may continue substitution with docetaxel if clinically appropriate. (Bristol-Myers Squibb, 2021a; Castells et al., 2022; Wilkes & Barton-Burke, 2020) |

(Continued on next page)

**TABLE 13-6.** Chemotherapy Drugs and Associated Acute Infusion-Related Reactions (*Continued*)

| Drug                     | Reaction Symptoms                                                                 | Frequency                                                                                                                                                                                                                                                                                                                                                                                     | Management                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Prevention                                                                                                                                                                                                                                                                                            |
|--------------------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Pegaspargase (Oncaspar®) | Urticaria, pruritus, angioedema, dyspnea, bronchospasm, laryngospasm, hypotension | 5%–8%, but increases to 33% after the fourth dose<br><br>Reactions may occur within minutes of administration; however delayed reactions are more common due to the slow release of the primary antigen.<br><br>Two preparations are available, <i>Escheri coli</i> and <i>Erwinia carotovora</i> , which are non-crossresistant. Other preparation can be substituted if the patient reacts. | Infusion-related reaction<br>• Stop drug.<br>• Treat symptoms with supportive care medications.<br>• After resolution of symptoms, consider restarting.<br><br>Anaphylaxis<br>• Stop drug.<br>• Treat for anaphylaxis.<br>• Do not rechallenge.<br>• Permanently discontinue use unless referred to an allergist.<br><br>The skin test is not validated. Some experts state the skin test is unreliable because of the high rate of false positives and false negatives. Desensitization protocols are available. | Premedications: antipyretic (optional), glucocorticoid (optional), H <sub>1</sub> and H <sub>2</sub> blocker<br><br>Premedications if prior reaction: glucocorticoid, H <sub>1</sub> and H <sub>2</sub> blocker (Castells et al., 2022; Sigma-Tau Pharmaceuticals, 2011; Wilkes & Barton-Burke, 2020) |

- (6) The European Society for Medical Oncology has published clinical criteria for diagnosing anaphylaxis. Familiarity with these criteria helps clinicians in the moment, when the patient requires epinephrine for anaphylaxis or impending anaphylaxis (Roselló et al., 2017; see Figure 13-3).

- (7) Anaphylactic reactions occur abruptly and can progress very quickly. This challenges the healthcare team to rapidly identify the nature of the reaction and the necessary treatment. Team familiarity with the criteria of anaphylaxis can facilitate clinical assessments and timely life-saving treatment.

*f) CRR and CRS*

- (1) CRR and CRS phenotypes are caused by the release of proinflammatory mediators, including tumor necrosis factor- $\alpha$ , interleukin-1- $\beta$ , and interleukin-6. Their endotypes include monocytes, macrophages, mast cells, and other immune cells with Fc- $\gamma$  receptors (Jimenez-Rodriguez et al., 2018).
- (2) CRR and CRS develop after cells are damaged and complement pathways are activated, resulting in a drastic increase in systemic inflammatory cytokines and interleukins (Cobb & Lee, 2021).
- (3) CRR describes an acute infusion-related reaction, which usually presents as mild or moderate and resolves with immedi-

ate treatment. CRS describes an acute and possible longer-term infusion-related reaction that generally presents as a severe, even life-threatening, systemic inflammatory reaction after the infusion of agents targeting the immune system, such as that seen in patients receiving chimeric antigen receptor (CAR) T-cell therapy. CRS typically requires more intensive interventions to resolve and may persist from hours to as late as seven days after completion of the infusion (Cobb & Lee, 2021; National Comprehensive Cancer Network, 2020). CRS may potentially result in organ failure or death (Cobb & Lee, 2021; LaCasce et al., 2021; Wilkes & Barton-Burke, 2020).

- (4) In most patients, the symptoms of CRR and CRS are less severe (National Comprehensive Cancer Network, 2020). Symptoms include mild fevers (days to weeks), tachycardia, chills, nausea, anorexia, myalgia, headache, rigors, and pain. If severe, symptoms can be life-threatening due to capillary leak, resulting in a third space fluid shift into the lungs and interstitial tissue and leading to intravascular depletion. Severe coagulopathy, with prolonged prothrombin time, partial thromboplastin time, and low fibrinogen levels, can occur with CRS, resulting in thrombocytopenia and an increased risk of thrombosis. Acute kidney injury can also occur due to hemo-

**TABLE 13-7.** Emergency Drugs for Use With Hypersensitivity or Anaphylactic Reactions

| Indication                                                                                    | Drug             | Dose                                                                                                                                                                                                                                                                                                                              | Comments                                                                                                                                                                                                                                                                                                                                                      |
|-----------------------------------------------------------------------------------------------|------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Bronchial constriction (e.g., dyspnea, wheezing, stridor)                                     | Epinephrine      | 0.1–0.5 mg IM into thigh (0.1–0.5 ml of 1:1,000 solution or EpiPen® 0.3 mg automatic device)<br>IV administration is indicated for patients with profound hypotension or signs or symptoms of impending shock who have not responded to IM dose.                                                                                  | IM administration is preferred over IV to minimize adverse cardiac effects.<br>Anterolateral upper thigh is preferable to deltoid (may also be administered by inhalation or subcutaneously).<br>Repeat every 5–10 minutes if needed.                                                                                                                         |
| Patients who do not respond after at least 2 doses of epinephrine and take a beta-blocker     | Glucagon         | 1 mg/50 ml IV over at least 5 minutes<br>Dose may be repeated up to 5 times for a total of 5 mg.<br>A continuous infusion may be indicated.<br>Consider a higher level of care if not responding.                                                                                                                                 | The drug is given preferably via IV pump at a controlled rate to minimize adverse effects of severe nausea and vomiting. If nausea and vomiting continue or occur even with a pump-controlled rate of administration, stop the drug.<br>Glucagon counteracts the systemic effects of anaphylaxis, as glucagon acts independently of alpha and beta receptors. |
| Shortness of breath, tachypnea (rate > 20 breaths per minute), or decreased oxygen saturation | Oxygen           | 2–6 L/min via a nasal cannula; 15 L via non-rebreather, if needed                                                                                                                                                                                                                                                                 | Patients who are hemodynamically unstable may also benefit from oxygen.                                                                                                                                                                                                                                                                                       |
|                                                                                               | Albuterol        | 2.5 mg/3 ml of 0.083% inhalation solution by nebulizer or 180 mcg (2 puffs) by metered-dose inhaler                                                                                                                                                                                                                               | Hold if heart rate is > 110 beats per minute.                                                                                                                                                                                                                                                                                                                 |
| Hypotension (> 30% decrease in systolic blood pressure from baseline)                         | Epinephrine      | Recommended dose is 0.01 mg/kg (maximum dose: 0.5 mg) IM into the antero-lateral thigh.<br>The dose should be drawn up using a 1 ml syringe using the 1 mg/ml formulation of epinephrine.<br>A single-dose vial is preferred.<br>The use of an autoinjector EpiPen (0.3 mg) is preferred for speed, reliability, and ease of use. | IM administration is preferred over IV to minimize adverse cardiac effects, except in the presence of cardiovascular collapse. Cardiac monitoring is recommended.                                                                                                                                                                                             |
|                                                                                               | Normal saline IV | 500 ml fluid bolus                                                                                                                                                                                                                                                                                                                | Administer over 10 minutes once and then as ordered.<br>Multiple fluid boluses may be required if the patient remains hypotensive despite epinephrine.<br>Massive fluid shifts can occur.                                                                                                                                                                     |
| Hives, itching, flushing, swollen lips or tongue                                              | Diphenhydramine  | 25–50 mg IVP                                                                                                                                                                                                                                                                                                                      | To counteract the multiple effects of histamine release, both H <sub>1</sub> and H <sub>2</sub> antagonists should be administered.                                                                                                                                                                                                                           |
|                                                                                               | Famotidine       | 20 mg IVP                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                               |
|                                                                                               | Ranitidine       | 50 mg IVP                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                               |
| Wheezing, cough, hives, or flushing                                                           | Montelukast      | 10 mg PO                                                                                                                                                                                                                                                                                                                          | The drug has an off-label use for infusion-related reactions.<br>It may be given as premedication.                                                                                                                                                                                                                                                            |
| Pain                                                                                          | Ketorolac        | 15 mg IVP                                                                                                                                                                                                                                                                                                                         | The drug is for the short-term management of moderately severe acute pain.                                                                                                                                                                                                                                                                                    |

(Continued on next page)

**TABLE 13-7.** Emergency Drugs for Use With Hypersensitivity or Anaphylactic Reactions (*Continued*)

| Indication                                                                                                 | Drug               | Dose                          | Comments                                                                                                                           |
|------------------------------------------------------------------------------------------------------------|--------------------|-------------------------------|------------------------------------------------------------------------------------------------------------------------------------|
| To prevent biphasic (delayed) reaction or for use with cytokine release reaction/cytokine release syndrome | Methylprednisolone | 40 mg IV (80 mg for > 120 kg) | A systematic review failed to find significant benefit in the initial prevention of anaphylaxis or as a delayed/biphasic reaction. |
|                                                                                                            | Hydrocortisone     | 100–500 mg IV                 |                                                                                                                                    |
|                                                                                                            | Dexamethasone      | 10–20 mg IV                   |                                                                                                                                    |

Additional emergency medications for advanced cardiovascular life support and emergency supplies (e.g., oxygen, suction machine with catheters, bag valve mask) should be available in a medical emergency.

IM—intramuscular; IV—intravenous; IVP—intravenous push

Note. Based on information from Campbell & Kelso, 2021; Castells et al., 2022; Commins, 2017; Galvão et al., 2017; Wilkes & Barton-Burke, 2020.

dynamic changes caused by a decrease in renal blood flow and glomerular filtration rate (Cobb & Lee, 2021).

- (5) Cancer treatments causing CRR usually include chimeric, humanized, and human monoclonal antibodies, such as rituximab and blinatumomab, and chemotherapy, such as oxaliplatin (Jimenez-Rodriguez et al., 2018). CRS is more often associated with CAR T-cell therapies (Cobb & Lee, 2021).

- g) Clinicians may find it challenging to determine what type of reaction a patient is having.

Using the precision medicine framework, acute infusion-related reactions may also be a mixture of type 1 HSR and CRR/CRS reactions. In this scenario, it is recommended to treat the reaction as a type 1 HSR.

- h) Using standardized scales to define reactions by grade helps to reduce the high variability in how reactions are reported. Clinical teams must be clear about which scale is used to ensure accurate assessment, communication, and documentation. Allergists have used the Brown grading system for generalized hypersensitivity reactions due to its clinical utility during the reac-

**TABLE 13-8.** Benefits of Epinephrine

| Benefit                                                                                     | Rationale                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|---------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Epinephrine is the most effective approach to preventing death from anaphylaxis.            | Epinephrine decreases the release of mediators of inflammation from mast cells and basophils.<br>Epinephrine prevents or reverses airflow obstruction in the upper and lower respiratory tracts and cardiovascular collapse.<br>Epinephrine increases vasoconstriction and peripheral vascular resistance.<br>Epinephrine decreases mucosal edema in the upper airway.<br>Epinephrine increases inotropy, chronotropy, and bronchodilation.<br>Antihistamines and glucocorticoids do not effectively treat anaphylaxis or prevent biphasic reactions. |
| No contraindications exist for giving epinephrine for anaphylaxis.                          | Recommended doses are effective with minor risks, as there is no other medication that can reliably reverse the lethal effects of anaphylaxis.                                                                                                                                                                                                                                                                                                                                                                                                        |
| Epinephrine given via the intramuscular route is more readily accessible than the IV route. | Giving epinephrine via the anterolateral upper thigh provides a rapid increase in plasma and tissue concentrations over the IV route. A lower risk exists for cardiovascular complications than with the IV route.                                                                                                                                                                                                                                                                                                                                    |
| Intramuscular dosing via autoinjector provides safer and more reliable dosing.              | Unfamiliarity with various epinephrine dilutions can lead to the wrong dosage. Autoinjectors have proved to eliminate dose variation when used following manufacturer instructions. If an autoinjector is not available, an institution must make a reliable plan for rapid and accurate administration of epinephrine.                                                                                                                                                                                                                               |
| Epinephrine is appropriate for anaphylaxis during pregnancy.                                | Some clinicians are reluctant to use epinephrine for anaphylaxis during pregnancy; however, it is the most effective treatment for anaphylaxis. Epinephrine may cause premature labor.                                                                                                                                                                                                                                                                                                                                                                |

Delayed administration of epinephrine is associated with fatalities.

Note. Based on information from Campbell & Kelso, 2021; Shaker et al., 2020.

**FIGURE 13-3.** European Society for Medical Oncology Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any one of the following three sets of criteria is fulfilled:

1. Acute onset of an illness (minutes to hours) with involvement of skin/mucous membranes (e.g., hives, generalized itch/flush, swollen lips/tongue/uvula) and at least one of the following:
  - a. Respiratory compromise (e.g., dyspnea, wheeze/bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
  - b. Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
  - a. Involvement of skin/mucous membranes (e.g., generalized hives, itch/flush, swollen lips/tongue/uvula)
  - b. Respiratory compromise (e.g., dyspnea, wheeze/bronchospasm, stridor, reduced peak expiratory flow, hypoxemia).
  - c. Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
  - d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced blood pressure after exposure to a known allergen for that patient (minutes to several hours); adult systolic blood pressure of < 90 mm Hg or > 30% decrease from that baseline

Note. Based on information from Roselló et al., 2017.

tion (Broyles et al., 2020; Fouda & Bavbek, 2020; Tsao et al., 2021). See Table 13-9 for the Brown grading system for generalized hypersensitivity reactions (Brown, 2004). See Table 13-10 for the National Cancer Institute Cancer Therapy Evaluation Program's *Common Terminology Criteria for Adverse Events* (CTCAE) for allergic reactions, anaphylaxis, and CRS. CTCAE criteria focus on the duration, severity, and interventions for the reaction. Although the Brown

grading system is not specific to the oncology population, it is focused on the specific symptoms commonly seen in HSRs (Tsao et al., 2021).

2. Risk factors for acute infusion-related reactions
  - a) Administration of a chemotherapy or immunotherapy agent known to cause HSRs
  - b) Drug versus vehicle: The vehicle in which the antineoplastic is dissolved (e.g., polysorbate 80, Cremophor) can be responsible for acute infusion-related reactions.
  - c) Access to health care, age, geography, industrialization, and preexisting allergies, such as food for young children, drugs for adolescents and adults, environmental allergens, and Hymenoptera venom (e.g., bees, yellow jackets, wasps, hornets) (Castells, 2017; Regateiro et al., 2020)
  - d) Premedication with fosaprepitant: Serious reactions, including anaphylaxis, have been reported with fosaprepitant and are thought to be related to the vehicle polysorbate 80. Do not resume use if symptoms occur with first-time administration (Hayes et al., 2021; Merck, 2019). Formulation substitutes do not contain polysorbate 80, and some institutions have substituted with IV aprepitant due to its favorable safety profile (Calcanes & Vacirca, 2019).
  - e) Previous exposure to the agent with mild symptoms of an allergic response
  - f) Failure to administer known effective prophylactic premedications
  - g) The first 5–15 minutes from the start of the infusion
  - h) The first infusion of rituximab (greater than 50% incidence) (LaCasce et al., 2021): “Priming the IV line with rituximab allows for a slow, incremental exposure, resulting in decreased hypersensitivity reaction incidence” (Laudati et al., 2018, p. 408).

**TABLE 13-9.** Brown Grading System for Generalized Hypersensitivity Reactions

| Grade      | Broad Clinical Features or Systems involved                                      | Defining Signs and Symptoms                                                                                                                                                         |
|------------|----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1–Mild     | Skin and subcutaneous tissues only                                               | Generalized erythema, urticaria, periorbital edema, angioedema                                                                                                                      |
| 2–Moderate | Features suggesting respiratory, cardiovascular, or gastrointestinal involvement | Dyspnea, stridor, wheeze, nausea, vomiting, dizziness (presyncope), diaphoresis, chest or throat tightness, abdominal pain                                                          |
| 3–Severe   | Hypoxia, hypotension, neurologic compromise                                      | Cyanosis, or blood oxygen saturation $\leq$ 92% at any stage of hypotension; systolic blood pressure < 90 mm Hg in adults; confusion; collapse; loss of consciousness; incontinence |

Mild reactions can be further subclassified into those with and without angioedema.

Note. Based on information from Brown, 2004.

**TABLE 13-10.** Common Terminology Criteria for Adverse Events Grading for Allergic Reaction, Anaphylaxis, and Cytokine Release Syndrome

| Adverse Event             | Grade                                         |                                                                              |                                                                                                                                       |                                                              |       |
|---------------------------|-----------------------------------------------|------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|-------|
|                           | 1                                             | 2                                                                            | 3                                                                                                                                     | 4                                                            | 5     |
| Allergic reaction         | Systemic intervention not indicated           | Oral intervention indicated                                                  | Bronchospasm; hospitalization indicated for clinical sequelae; IV intervention indicated                                              | Life-threatening consequences; urgent intervention indicated | Death |
| Anaphylaxis               | —                                             | —                                                                            | Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension | Life-threatening consequences; urgent intervention indicated | Death |
| Cytokine release syndrome | Fever with or without constitutional symptoms | Hypotension responding to fluids; hypoxia responding to < 40% O <sub>2</sub> | Hypotension managed with one pressor; hypoxia requiring ≥ 40% O <sub>2</sub>                                                          | Life-threatening consequences; urgent intervention indicated | Death |

IV—intravenous; O<sub>2</sub>—oxygen

Note. From *Common Terminology Criteria for Adverse Events* [v.5.0], by National Cancer Institute Cancer Therapy Evaluation Program, 2017 ([https://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/docs/CTCAE\\_v5\\_Quick\\_Reference\\_5x7.pdf](https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf)). In the public domain.

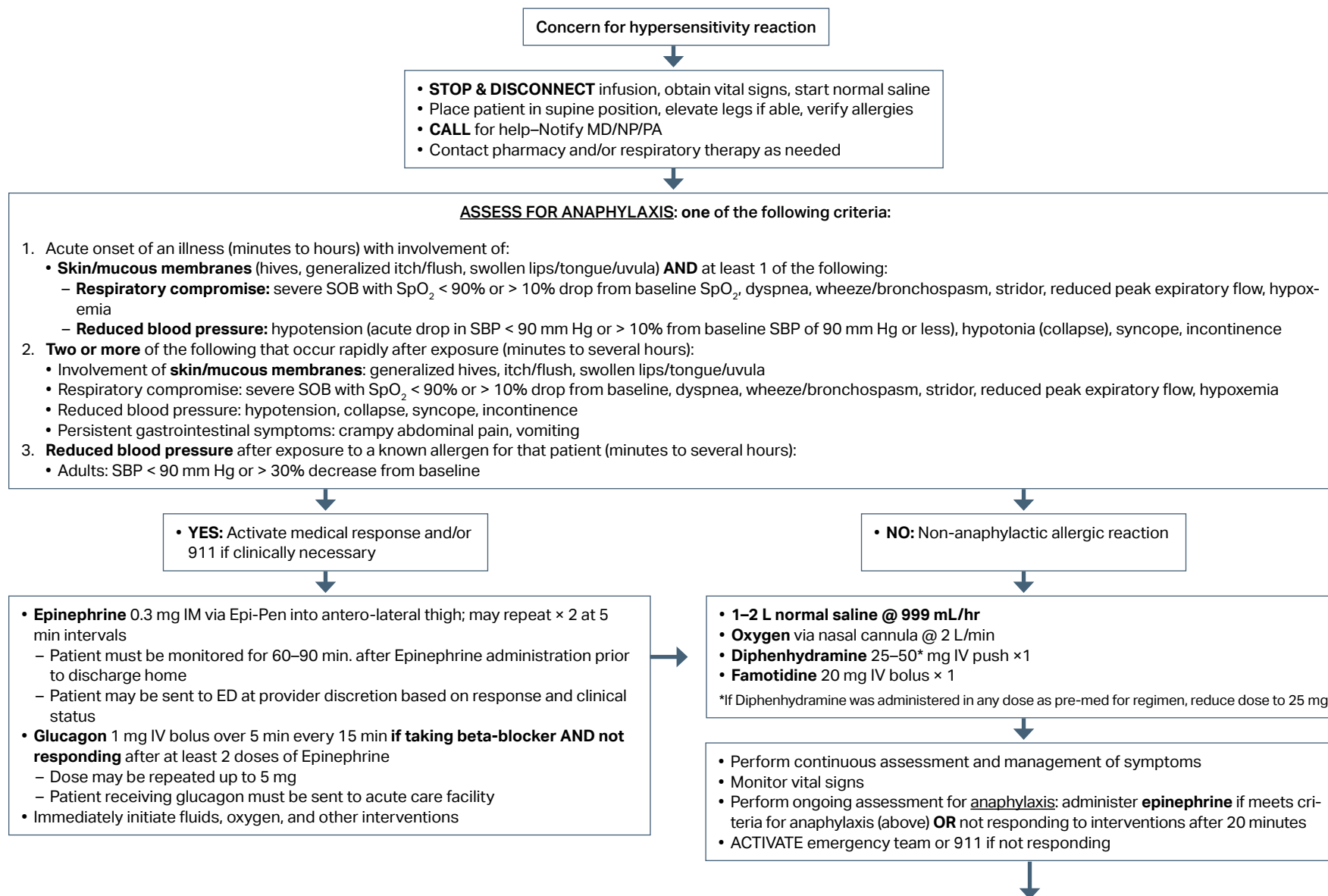
- i) Patients with leukemia or lymphoma, especially those with high tumor/lymphocyte counts (greater than 25,000/mm<sup>3</sup>) (Wilkes & Barton-Burke, 2020)
  - j) Nurses in infusion units should confirm allergy history prior to drug administration and observe patients closely for acute infusion-related reactions. Patients need education to self-report symptoms of a reaction immediately. Failure of staff to identify early symptoms of a reaction and a lack of patient self-report may contribute to a delay in identifying a reaction and interventions for treatment (Hayes et al., 2021; Rombouts et al., 2020).
3. Risk factors for CRR/CRS
- a) Monoclonal antibodies
  - b) CAR T-cell therapy is a form of immunotherapy using genetically modified T cells to produce CARs. The T cells are isolated and modified using a retroviral or lentiviral vector. Depending on the indication, CAR T cells target a specific antigen expressed on malignant cells (e.g., cluster of differentiation 19) to cause apoptosis.
    - (1) CRR/CRS is the main complication experienced after the cell infusion and is caused by the release of interleukin-6, leading to systemic inflammation. It is seen as early as day 0 and should be anticipated with CAR-T cell therapy (Wei et al., 2020).
    - (2) Nurses caring for patients during CAR T-cell therapy need to have specific education and competency validation, given the severity of CRR/CRS, the intensity of the treatments, and the evolving approaches for identifying and managing CAR T-cell–related CRR/CRS.
    - (3) As of this writing, agents approved for CAR T-cell therapy with a black box warning for reactions and CRR/CRS, among other complications, include the following:
      - (a) Abecma® (idecabtagene vicleucel) (Celgene, 2021)
      - (b) Breyanzi® (lisocabtagene maraleucel) (Juno Therapeutics & Bristol Myers Squibb, 2021)
      - (c) Kymriah® (tisagenlecleucel) (Novartis Pharmaceuticals, 2022)
      - (d) Tecartus® (brexucabtagene autoleucel) (Kite Pharma, 2022a)
      - (e) Yescarta® (axicabtagene ciloleucel) (Kite Pharma, 2022b)
    - (4) For treatment of CRR/CRS, it is recommended to administer tocilizumab or combination tocilizumab and a cortico-



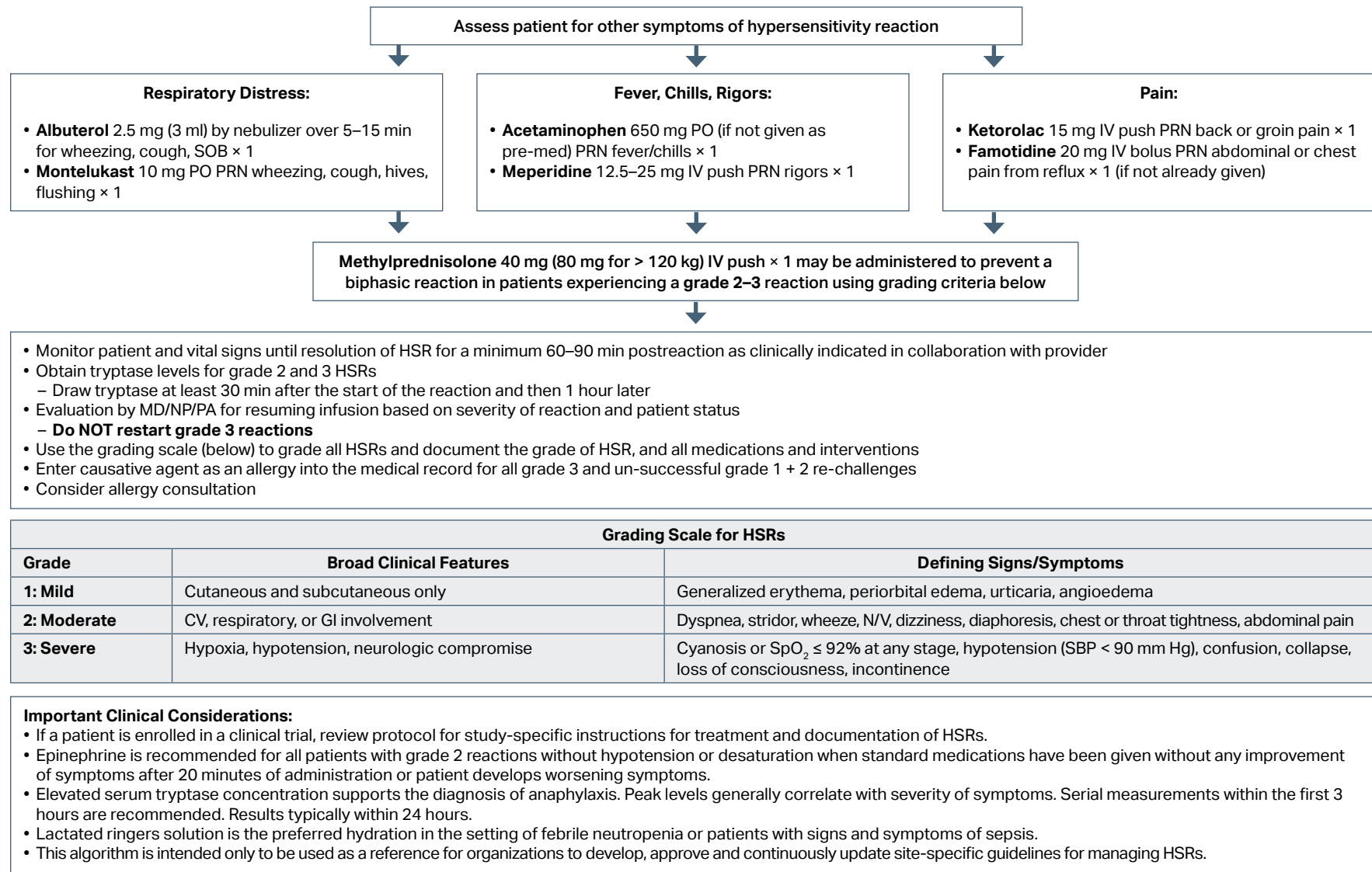
- steroid. Tocilizumab targets interleukin-6 and resolves symptoms within 24–48 hours (Genentech, 2021). The early administration of tocilizumab can prevent CRR/CRS without compromising the efficacy of CAR T-cell therapy (Kadauke et al., 2019).
4. Implement the following steps to identify, prevent, and manage acute infusion-related reactions following evidence-based medical, pharmacologic, and nursing references and institutional standards of practice.
    - a) Obtain and record baseline vital signs, height and weight, and patient assessment findings.
    - b) Perform a thorough pretreatment patient assessment to verify recovery from past treatment, consent to treatment, and the need to reinforce key education about the treatment. A chart review includes but is not limited to diagnosis, regimen/treatment plan, previous doses administered (e.g., premedications), dose modifications/delays, tolerance and reactions to past treatments, current cycle/day, cycle length, IV access, history of any category of acute infusion-related reaction, allergy history (e.g., food, medication, environment), and criteria to treat (including laboratory tests).
    - c) Review the medication list to identify a beta-blocker.
      - (1) Beta-blockers can inhibit the response to epinephrine in anaphylaxis. If patients do not respond after two doses of epinephrine and are taking a beta-blocker, 1 mg IV glucagon over at least five minutes (see Table 13-8) can exert inotropic and chronotropic effects. This counteracts the systemic effects of anaphylaxis, as glucagon acts independently of alpha and beta receptors (Campbell & Kelso, 2021).
      - (2) See Table 13-7 for more information on administration considerations. Failure to respond to two doses of epinephrine is also a possible indicator of the need for a higher level of care.
    - d) Administer premedications as ordered per institutional standards and as recommended per package insert.
      - (1) Common premedications include histamine antagonists (e.g., H<sub>1</sub> antagonist [diphenhydramine], H<sub>2</sub> antagonist [ranitidine or famotidine]), acetaminophen, and glucocorticoids (LaCasce et al., 2021).
      - (2) Peak action of oral versus IV routes can vary, and appropriate timing of premedications prior to treatment should be considered.
  - (3) Premedications do not fully protect patients from anaphylaxis (Shaker et al., 2020).
  - e) Ensure clinicians, including nurses, physicians, and advanced practice providers, are present in the infusion setting and that emergency equipment and medications are readily available. These clinicians must be competent in managing acute infusion-related reactions and providing basic life support (Neuss et al., 2017).
  - f) Obtain provider orders for emergency treatment before drug administration. Given that medications used in the oncology setting may lead to acute infusion-related reactions, written standing orders for managing acute infusion reactions are recommended, along with specific role delineation and interventions for each clinician to ensure an immediate, organized, and competent response (Commings, 2017).
  - g) With each infusion, instruct patients to report symptoms of hypersensitivity and infusion reaction immediately while concurrently visualizing and eliciting self-report of symptoms.
  - h) Monitoring for reactions in unique situations
    - (1) Acute infusion-related reactions can occur with repeated exposure to a drug and at any time during the infusion or the treatment cycle. Most reactions occur during the first or second exposure (LaCasce et al., 2021; Rombouts et al., 2020).
    - (2) Approximately 10%–30% of reactions will occur after the second exposure.
      - (a) For example, the incidence of an acute infusion-related reaction with a platinum-containing agent increases with multiple doses and can occur after the infusion has been completed (Castells et al., 2022; LaCasce et al., 2021).
      - (b) No data exist to support routine premedications prior to all cycles of platinum agents in the absence of prior reaction.
      - (c) Although it is reasonable to consider premedications or the administration of incremental doses of an IV drug from low to the maximum rate, known as titration, for patients receiving cycle 5 or beyond of a platinum-containing agent, the determination is made on a case-by-case basis (Castells et al., 2022).
    - (3) Patients with a *BRCA1/2* variant experience more immediate acute infusion reac-



- tions than those without a *BRCA1/2* variant and require close monitoring for reaction (Galvão et al., 2017).
- (4) Acute laryngopharyngeal dysesthesia, a rapid onset of cold-related sensations of dyspnea, difficulty swallowing or talking, jaw contraction, and odd sensations in the tongue and pharynx, may occur during or after an oxaliplatin infusion. It may be clinically indistinguishable from an acute infusion-related reaction (Pachman et al., 2015).
  - (5) Irinotecan-induced cholinergic syndrome is well known and may present during and within the first 24 hours of administration. It is characterized by diarrhea, abdominal cramping, emesis, diaphoresis, and, less commonly, hyperlacrimation and rhinorrhea. This syndrome may be clinically indistinguishable from an acute infusion-related reaction (Roselló et al., 2017).
  - (6) Complement activation-related pseudo-allergy (CARPA) is a non-IgE reaction that often presents with the first or second dose.
    - (a) It can range in severity, including anaphylaxis, and is managed as a type 1 HSR.
    - (b) CARPA has been associated with the vehicles Cremophor or polysorbate 80 found in taxanes, fosaprepitant, cyclosporine, diazepam, propofol, and vitamin K (Castells et al., 2022; Eisenberg, 2018).
    - (c) The first reaction is often worse and diminishes with subsequent exposures. Grade 3 reactions would indicate discontinuation before any additional doses are given, and referral to an allergist may be indicated to continue (Cáceres et al., 2019; D'Errico et al., 2020).
  - (7) Paclitaxel standard premedications, including glucocorticoid,  $H_1$  and  $H_2$  blockers, help decrease the severity of the reaction when given 30–60 minutes prior to therapy administration.
    - (a) In the absence of a reaction, dose reduction or discontinuation of all premedications after two infusions is safe and effective in preventing paclitaxel-related reactions (Yenilmez et al., 2017).
    - (b) Little evidence supports titration of paclitaxel to minimize HSR risk.
    - (c) Nymberg et al. (2021) noted titration to be associated with an increased rate of subsequent emergency medicine use compared to maintaining a set infusion rate after experiencing a reaction. More evidence surrounding paclitaxel titration is needed to guide safe practice recommendations.
    - (d) Titration can be considered a form of desensitization and needs to be planned and performed within a well-defined setting using an inter-professional approach to ensure safety.
    - (e) To reduce the incidence of infusing a Cremophor bolus, double invert the bag gently prior to administration to ensure even distribution (Castells et al., 2022).
  - (8) For patients who have successfully received and tolerated the first full dose of rituximab without a grade 3–4 acute infusion-related reaction (among other exclusion criteria), subsequent rituximab infusions may be administered at an initial rate of 20% of the total dose over 30 minutes. This is followed by the remaining 80% over 60 minutes, known as a rapid infusion. In the event of a grade 3–4 reaction, patients are not eligible for rapid infusion until they have received standard infusion rituximab without any reaction (Genentech, 2010b).
5. Clinical management of acute infusion-related reactions: Assess and treat symptoms as quickly as possible. Respiratory or cardiac arrest and death can occur within several minutes; therefore, a rapid, competent, standardized team response is required for optimal management and outcomes. Figure 13-4 provides a guide for treating acute infusion-related reactions based on grade.
- a) Stop drug infusion immediately and disconnect the allergen, noting the reaction start time.
  - b) Maintain an IV line with normal saline infusing wide open.
  - c) Call for help.
  - d) Stay with the patient and verify allergies. Request another team member to notify the provider and emergency team with pertinent details (i.e., name, location, problem, and status, including vital signs and concerns). Local emergency medical services should be called and provided with the same pertinent details if outside the hospital setting.

**FIGURE 13-4.** Infusion-Related Toxicity Algorithm

(Continued on next page)

**FIGURE 13-4.** Infusion-Related Toxicity Algorithm (*Continued*)

CV—cardiovascular; ED—emergency department; GI—gastrointestinal; HSR—hypersensitivity reaction; IV—intravenous; MD—medical doctor; N/V—nausea/vomiting; NP—nurse practitioner; PA—physician assistant; PO—by mouth; PRN—as needed; SBP—systolic blood pressure; SOB—shortness of breath; SpO<sub>2</sub>—oxygen saturation

Note. Based on information from Brown, 2004; Campbell & Kelso, 2020, 2021; Castells et al., 2022; Commins, 2017; Galvão et al., 2017; Roselló et al., 2017; Shaker et al., 2020; Wilkes & Barton-Burke, 2020.

Figure courtesy of Dana-Farber Cancer Institute. Adapted with permission.

- e) Maintain the patient upright if short of breath or vomiting. Place the patient in a supine position, if able, and elevate the legs if hypotensive (systolic blood pressure less than 60 mm Hg).
- f) Monitor vital signs (i.e., temperature, pulse, respiration, blood pressure, and oxygen saturation) as clinically appropriate until resolution (60–90 minutes postreaction). Consider an electrocardiogram if appropriate for the level of care and staff competency. Consider transfer to a higher level of care to monitor for significant cardiac changes.
- g) Maintain airway, assessing the patient for increasing respiratory tract edema, shortness of breath, and dyspnea. Administer oxygen if needed. Anticipate the need for CPR. Initiate basic life support as indicated.
- h) Observe for and evaluate symptoms.
  - (1) For grade 1–2 reactions, administer an  $H_1$  and  $H_2$  blocker.
    - (a) Treat symptoms with additional supportive care medications as indicated.
    - (b) Observe the patient until symptoms resolve, usually within 30 minutes. After the resolution of symptoms, review manufacturer instructions for additional recommendations, such as rate titrations.
    - (c) Continue ongoing assessment for signs and symptoms of acute infusion-related reaction or advancement to anaphylaxis.
    - (d) If symptoms are not resolving or worsening, prepare to administer epinephrine and activate the emergency team or local emergency services.
  - (2) For grade 3 reactions or when symptoms are worsening or not resolving, administer emergency medications based on symptoms, starting with epinephrine, and activate the emergency team or local emergency services (Campbell & Kelso, 2021; Commins, 2017).
    - (a) Because anaphylaxis is potentially life threatening, it needs to be identified immediately and treated with epinephrine, the only medication that can reverse life-threatening symptoms of anaphylaxis (see Table 13-8).
    - (b) Do not restart the causative agent with grade 3 reactions. Observe the patient until stabilized. Disposition is determined based on the severity of the reaction, patient recovery after treatment, and comorbidities. Consider referral to an allergist for desensitization.
- i) Provide emotional support to the patient and family.
- j) Document all treatments, the grade of reaction using an institution-approved hypersensitivity grading scale, and the patient's response to interventions in the medical record. Note the time the reaction started and the time tryptase levels are to be drawn (as ordered and if available) to determine the need for desensitization and assist the allergist in assessing and determining the reaction etiology at a future time.
- k) Document causative agent as an allergy in the medical record regardless of the grade of reaction.
- l) Consider allergist consult or referral to desensitization clinic.
- m) Debriefing should occur as soon as possible after an acute infusion-related reaction to review provided care, clinical decisions, team performance, and opportunities for improvement (Patient Safety Network, 2021).
- n) Known as a biphasic reaction, symptoms of anaphylaxis may recur hours after the initial intervention. Although etiology and incidence are not fully understood, consider administering a glucocorticoid (methylprednisolone 40 mg IV push [80 mg for greater than 120 kg]) for patients experiencing a grade 2 or higher reaction. A recent systematic review failed to find significant benefit to steroid use in the initial prevention of anaphylaxis or as a delayed/biphasic reaction (Campbell & Kelso, 2021; Shaker et al., 2020).
- o) Monitor the patient until symptoms of anaphylaxis have fully resolved.
  - (1) No consensus exists on the required observation time.
  - (2) Patients with severe anaphylaxis and those who require more than one dose of epinephrine are at an increased risk for a biphasic reaction; therefore, emergency department monitoring or hospital admission should be considered (Campbell & Kelso, 2021).
- p) For patients who experience a suspected anaphylactic reaction, a tryptase blood level should be drawn (as ordered and if available) no sooner than 30 minutes from the start of the reaction and again 60 minutes after the first tryptase level is drawn. If an urgent transfer is required, attempt to draw one tryptase prior to transfer to ensure sensitivity and specificity as levels peak

30–90 minutes after the onset of anaphylaxis (Schwartz, 2020).

- (1) Any elevation in serum total tryptase is consistent with anaphylaxis; however, a normal value does not exclude anaphylaxis because it may be a false negative based on the timing of the draw or may need to be compared to a baseline level.

- (a) The sample should not be drawn at the onset of the symptoms to reduce the risk of a false-positive result (Schwartz, 2020).

- (b) Results of tryptase levels drawn during the acute phase are only useful when viewed with additional postreaction values and other clinical data to capture the patient's trending and complete clinical picture.

- (c) Tryptase levels are intended only to augment postreaction assessment and interventions by the allergist for the possible benefit of a desensitization plan (Campbell & Kelso, 2020).

- (d) Elevation of serum tryptase levels is consistent with anaphylaxis, but one normal tryptase level cannot exclude anaphylaxis (Castells et al., 2022).

- (2) Avoid administering subsequent doses of the causative agent if the patient is to be desensitized to the drug.

- (a) Drug desensitization is a controlled reexposure to the causative agent to produce a temporary tolerance, allowing the patient to safely receive an uninterrupted course (Castells & Solensky, 2020).

- (b) If the drug is critical to the treatment plan, refer the patient to an allergist qualified in drug desensitization (Castells et al., 2022).

- (c) Drug desensitization is recommended after showing that the benefits outweigh the risks. It should be used with caution by competent nurses and providers under the guidance of an allergist when available (Castells et al., 2022).

## 6. Skin testing

- a) Skin testing using the prick/puncture and intradermal methods may be performed in collaboration with a qualified allergist on patients four to six weeks after they experienced an infusion-related reaction with any symptom suggestive of possible anaphylaxis (Castells et al., 2022; Jimenez-Rodriguez et al., 2018).

- b) It has limited value with most chemotherapy except for platinum-containing drugs and taxanes (Fouda & Bavek, 2020; Tsao et al., 2021).

- c) This practice is valuable because it evaluates whether patients are truly allergic to the drug or class.

- d) Skin testing for other drugs is considered investigational and not widely performed. Skin testing with vesicants is not to be performed. Testing with irritants must be performed carefully with dilution and a qualified allergist (Castells et al., 2022).

- e) Only allergists with special training in technique, interpretation, and management of rare allergic reactions should perform these tests in highly sensitive patients because of the risk of dermatologic or other toxicities associated with chemotherapy skin testing (Castells et al., 2022).

- f) Minimal data are available for skin testing with immunotherapy agents. Few allergy centers associated with oncology practices have experience with skin testing (Khan, 2016; LaCasce et al., 2021).

## F. Patient and caregiver education

1. Before therapy, inform patients and families that chemotherapy and immunotherapy agents have the potential for acute infusion-related reactions. Instruct them to report signs and symptoms immediately.
2. After infusion, instruct patients and families about the importance of immediately reporting symptoms of any delayed reaction. If a reaction is experienced, include the drug on their allergy list in the medical record to prevent future inadvertent administration.
3. Document all patient teaching and interventions.

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## SECTION V

# Treatment-Related Complications

- Chapter 14. Myelosuppression
- Chapter 15. Gastrointestinal and Mucosal Toxicities
- Chapter 16. Cardiovascular Toxicities
- Chapter 17. Pulmonary Toxicities
- Chapter 18. Hepatic Toxicities
- Chapter 19. Genitourinary Toxicities
- Chapter 20. Altered Sexual and Reproductive Functioning
- Chapter 21. Cutaneous Toxicities and Alopecia
- Chapter 22. Endocrine Toxicities
- Chapter 23. Fatigue
- Chapter 24. Neurologic Toxicities
- Chapter 25. Ocular Toxicities



## CHAPTER 14

# Myelosuppression

### A. Overview

1. Myelosuppression is a condition manifested by a significant decrease in the neutrophils, megakaryocytes, and erythrocytes within the bone marrow (National Cancer Institute [NCI], n.d.). It is a dose-limiting toxicity of systemic chemotherapy (Camp-Sorrell, 2018).

#### a) Neutropenia

- (1) Neutropenia is defined as a significant reduction in the absolute number of circulating neutrophils in the blood.
- (2) The absolute neutrophil count (ANC) is the basis for neutropenia classification and is generally defined as an ANC less than  $1,500/\text{mm}^3$  (Territo, 2021).
- (3) The National Comprehensive Cancer Network (NCCN, 2021c) defines febrile neutropenia as an ANC less than  $500/\text{mm}^3$  or the expectation that the neutrophil count will decline to less than  $500/\text{mm}^3$  within 48 hours.
- (4) The *Common Terminology Criteria for Adverse Events* stratifies grades of febrile neutropenia (NCI Cancer Therapy Evaluation Program, 2017; see Table 14-1).
- (5) Stratifying the severity of neutropenia related to relative infection risk helps identify those at risk following myelosuppressive therapy (NCCN, 2021c; NCI, 2017; Territo, 2021).
  - (a) Mild: ANC  $1000\text{--}1,500/\text{mm}^3$
  - (b) Moderate: ANC less than  $500\text{--}1,000/\text{mm}^3$
  - (c) Severe: ANC less than  $500/\text{mm}^3$

#### b) Anemia

- (1) In adults with cancer, hemoglobin (Hgb) of 10 g/dl or lower or 2 g/dl or greater below baseline warrants evaluation for anemia (NCCN, 2021).
- (2) Other references for adults in industrialized nations identify 14 g/dl for men and

12 g/dl for women as lower limits for normal Hgb (Braunstein, 2020).

- (3) A decrease in the hematocrit or number of red blood cells (RBCs) can be used to define anemia. Still, Hgb is used most often because it reflects the physiologic consequences of anemia (Braunstein, 2020).

c) Thrombocytopenia is a platelet count below the lower limit of normal  $140,000\text{--}400,000/\text{mm}^3$  (Kuter, 2020).

d) Cytopenia is a condition marked by lower-than-normal blood cell counts (NCI, n.d.).

e) Pancytopenia is a lower than normal number of RBCs, white blood cells (WBCs), and platelets (NCI, n.d.).

f) The nadir is the time or level at which the lowest blood cell count is reached following cytotoxic therapy. It varies with individual agents but usually occurs 7–10 days after treatment (Cancer.Net Editorial Board, 2019).

#### g) Hematopoiesis

- (1) Hematopoiesis is the production of all blood cells from hematopoietic stem cells (HSCs) (NCI, n.d.). Most hematopoiesis occurs in the bone marrow in myeloid tissues of adults (see Figure 14-1).

- (2) The process begins with HSCs (also known as pluripotent stem cells) (NCI, n.d.).

(a) These are the most primitive type of blood cells and the source of all HSCs.

(b) HSCs can self-renew and maintain their numbers because they can proliferate, differentiate, and mature into all cell lines.

(c) With each stem cell division, one daughter cell stays in the stem cell pool, whereas the other daughter cell leaves the stem cell pool and becomes committed to a distinct cell line.

**TABLE 14-1.** Common Terminology Criteria for Adverse Events Grading for Anemia, Neutropenia, and Thrombocytopenia

| Adverse Event               | Grade                                                           |                                                                   |                                                                                                                                                          |                                                                       |       |
|-----------------------------|-----------------------------------------------------------------|-------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------|-------|
|                             | 1                                                               | 2                                                                 | 3                                                                                                                                                        | 4                                                                     | 5     |
| Anemia                      | Hgb < LLN–10 g/dl;<br>< LLN–6.2 mmol/L;<br>< LLN–100 g/L        | Hgb < 10–8 g/dl;<br>< 6.2–4.9 mmol/L; <<br>100–80 g/L             | Hgb < 8 g/dl; < 4.9 mmol/L;<br>< 80 g/L; transfusion indi-<br>cated                                                                                      | Life-threatening<br>consequences;<br>urgent intervention<br>indicated | Death |
| Decreased<br>platelet count | < LLN–75,000/mm <sup>3</sup> ;<br>< LLN–75 × 10 <sup>9</sup> /L | < 75,000–50,000/mm <sup>3</sup> ;<br>< 75–50 × 10 <sup>9</sup> /L | < 50,000–25,000/mm <sup>3</sup> ;<br>< 50–25 × 10 <sup>9</sup> /L                                                                                        | < 25,000/mm <sup>3</sup> ;<br>< 25 × 10 <sup>9</sup> /L               | –     |
| Febrile neu-<br>tropenia    | –                                                               | –                                                                 | ANC < 1,000/mm <sup>3</sup> with<br>a single temperature ><br>38.3°C (101°F) or a sus-<br>tained temperature ≥ 38°C<br>(100.4°F) for more than 1<br>hour | Life-threatening<br>consequences;<br>urgent intervention<br>indicated | Death |

ANC—absolute neutrophil count; Hgb—hemoglobin; LLN—lower limit of normal

Note. From *Common Terminology Criteria for Adverse Events* [v.5.0], by National Cancer Institute Cancer Therapy Evaluation Program, 2017 ([https://ctep.cancer.gov/protocoldevelopment/electronic\\_applications/docs/CTCAE\\_v5\\_Quick\\_Reference\\_5x7.pdf](https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf)). In the public domain.

(d) These committed progenitor cells differentiate and mature in the bone marrow.

(e) Whether HSCs proliferate or differentiate is determined by the body's needs in response to exogenous (e.g., high altitude) or endogenous (e.g., stress, infection, hemorrhage, drug therapy) influences. Once released into the bloodstream, mature cells have a varied life span (see Table 14-2).

2. Most chemotherapy agents cause some degree of myelosuppression (Zack, 2018). The degree and duration of chemotherapy-related myelosuppression are related to the agent's mechanism of action (e.g., cell cycle-specific drugs are associated with rapid cytopenias) and dose intensity (NCCN, 2021).

## B. Types of cytopenias

### 1. Neutropenia in patients with cancer

a) Chemotherapy-induced neutropenia is the primary dose-limiting toxicity associated with systemic chemotherapy (Zack, 2018). It has significant negative clinical consequences for patients with cancer, including life-threatening infections, prolonged hospital stays, dose reductions, and dose delays (NCCN, 2021).

b) Healthy physiology of neutrophils

- (1) Neutrophils differentiate from pluripotent stem cells and continue a maturation process in the bone marrow. After differentia-

tion, these cells progress from myeloblast to promyelocyte, myelocyte, and then metamyelocyte. Ultimately, they transform into nearly mature bands and segmented neutrophils.

- (2) This process takes approximately two weeks.

- (3) The segmented neutrophils and bands (when required) are released from the bone marrow into the bloodstream, where they live for approximately 12 hours (Mahdi, 2018; Wilson, 2018).

c) Locations of neutrophils (Rosales, 2018)

- (1) The bone marrow of a healthy adult contains mature segmented neutrophils and immature neutrophils in various stages of development. Neutrophils leave the bone marrow for the blood through pores that form between the marrow parenchyma and venous blood vessels.

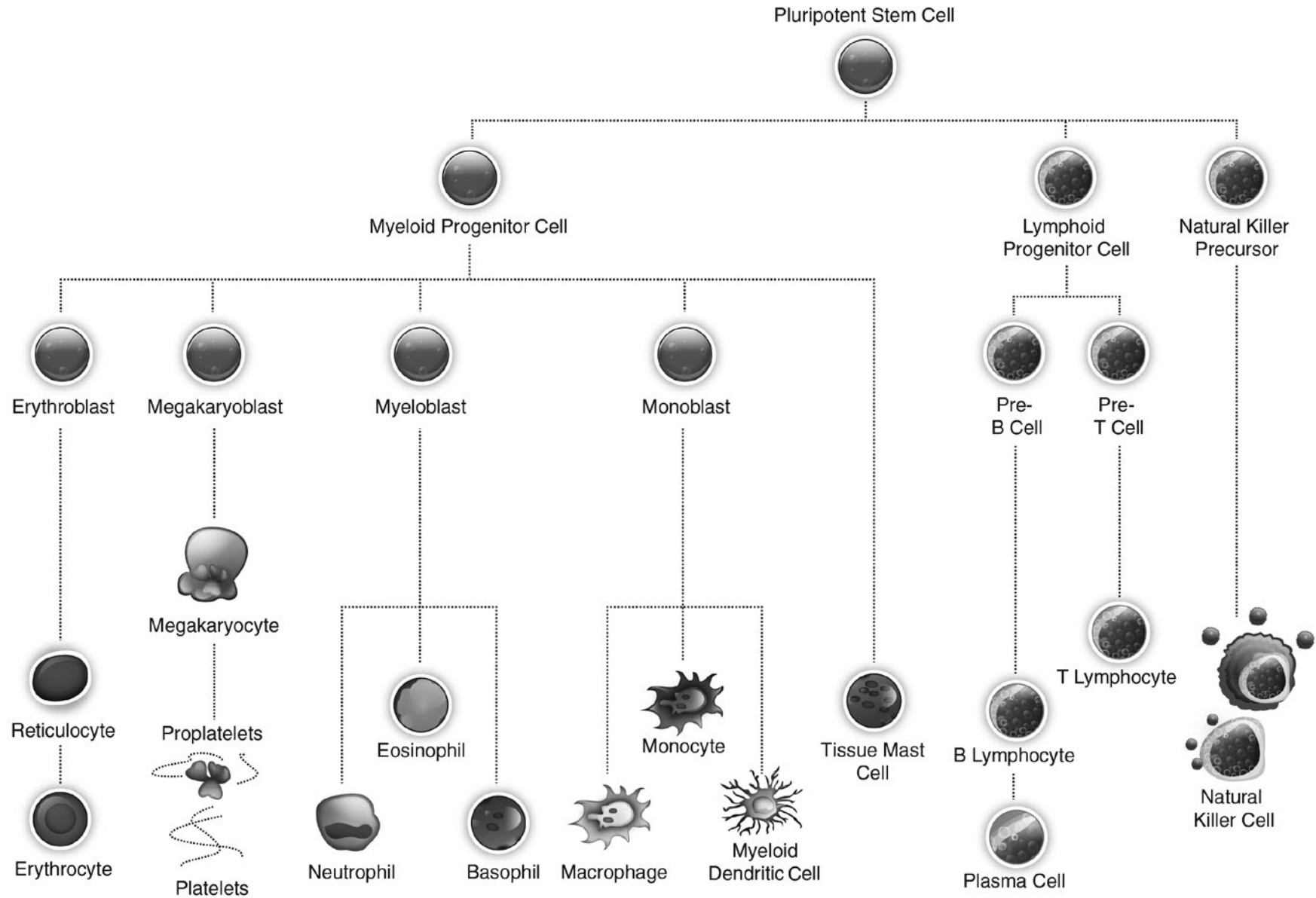
- (2) Once in the bloodstream, these cells join the functional pool by circulating or lining blood vessel walls as marginated cells, meaning they adhere to endothelial cells lining the blood vessel.

- (3) Neutrophils exist in the bloodstream as mature and immature cells. These cells perform a critical role in the body's defense.

- (4) The result is the activation of neutrophil defense and movement of neutrophils to the site of infection (Rosales, 2018).



**FIGURE 14-1.** Hematopoiesis and Cytokine Delineation



Note. Copyright 2014 by Oncology Nursing Society. Used with permission.

**TABLE 14-2.** Life Spans of Blood Components

| Blood Component     | Typical Life Span                          |
|---------------------|--------------------------------------------|
| Red blood cell      | 90–120 days                                |
| Platelet            | 8–10 days                                  |
| Neutrophil          | < 48 hours                                 |
| Monocyte            | 5 days, but depends on many factors        |
| Macrophage          | Depends on many factors                    |
| Eosinophil          | 8–18 hours in blood and 2–5 days in tissue |
| Basophil            | 1–2 days                                   |
| Tissue mast cell    | Cutaneous: 1 year; mucosal: 1–2 weeks      |
| B lymphocyte        | Depends on type and subtype                |
| T lymphocyte        | Depends on type and subtype                |
| Natural killer cell | Approximately 10 days                      |

Note. Based on information from Kitamura, 1989; Milot & Filep, 2011; Min et al., 2012; Nayak et al., 2013; Park & Bochner, 2010; Pillay et al., 2010; Whitelaw, 1966; Zhang et al., 2007.

- (5) Neutrophils leave the blood for tissue by migrating through endothelial cells. After functioning in the tissue, neutrophils succumb to apoptosis and are phagocytized by macrophages (Rosales, 2018).

d) Pathophysiology

- (1) The bone marrow must constantly produce neutrophils because their life span is estimated to be less than 48 hours.
  - (a) Chemotherapy agents suppress bone marrow activity and damage stem cells, preventing them from continuing the maturation process.
  - (b) Therefore, chemotherapy decreases the neutrophil count as mature neutrophils die and are not replaced (Camp-Sorrell, 2018).
- (2) WBC nadir depends on the specific drugs and dosages used.
  - (a) Chemotherapy regimens that also include monoclonal antibodies (mAbs) have the potential to increase the risk of febrile neutropenia (NCCN, 2022c).
  - (b) The mAb conjugates (e.g., sacituzumab govitecan-hziy) can also put patients at risk for severe neutropenia (Immunomedics, 2021; see Chapter 9).

- i. Cell cycle-specific agents (e.g., antimetabolites) are generally less damaging because they primarily affect cells in a specific phase of the cell cycle. Severe neutropenia can develop when cell cycle-specific drugs are used in dose-intensification and combination chemotherapy regimens (Tortorice, 2018).
- ii. Cell cycle-nonspecific agents (e.g., alkylating agents, nitrosoureas) damage cells in all phases of the cell cycle, thereby causing more damage to stem cells. The extent of neutropenia with these agents is dependent on dose, schedule, and agent. For example, oxaliplatin as a single agent is expected to cause mild neutropenia, but toxicity can be much higher in regimens with 5-fluorouracil and leucovorin (Tortorice, 2018).
- iii. Some cell cycle-nonspecific agents (e.g., carmustine) produce delayed and prolonged neutropenia. Nadir occurs at three to five weeks in adults, with recovery as long as five to six weeks (Ben Venue Laboratories, 2007).

- e) Fever and febrile neutropenia: Fever is defined as a one-time oral temperature greater than 101°F (38.3°C) or oral temperature of 100.4°F (38°C) lasting one hour. Febrile neutropenia occurs when ANC is less than 500/mm<sup>3</sup> or less than 1,000/mm<sup>3</sup> with an anticipated decline to 500/mm<sup>3</sup> or less over the next 48 hours with fever (NCCN, 2021, 2022c).

f) Risk assessment

- (1) Febrile neutropenia risk should be assessed prior to the first and each subsequent treatment cycle (NCCN, 2021; Wilson et al., 2019). Increased infection risk is present in patients with fever (Taplitz et al., 2018).
- (2) Risk factors for developing febrile neutropenia in adults being treated for solid tumors (NCCN, 2022c; see Figure 14-2)
  - (a) Age 65 years or older receiving chemotherapy dose intensity
  - (b) Persistent neutropenia

**FIGURE 14-2.** Risk Factors for Developing Febrile Neutropenia**Patient Related**

- Age > 65 years
- Assigned gender female
- Poor performance status
- Poor nutritional status
- Low neutrophil count at the beginning of a treatment cycle
- Renal dysfunction
- Liver dysfunction, especially elevated bilirubin
- Cardiovascular disease
- Recent surgery
- Preexisting infection
- Open wounds

**Disease Related**

- Advanced disease stage
- Tumor involvement of the bone marrow
- Type of malignancy: hematologic (e.g., leukemia, myelodysplastic syndromes), breast, lung, colorectal, ovarian, and lymphoma
- Preexisting, prolonged, or previous episode of neutropenia

**Treatment Related**

- Previous myelosuppressive chemotherapy or radiation
- Treatment intent (curative intent rather than palliative)
- Planned relative dose intensity ( $\geq 85\%$ )
- Use of specific medications (e.g., immunosuppressive drugs)
- Chemotherapy intensity (i.e., dose dense, high dose, myeloablative)

Note. Based on information from Freifeld et al., 2011; National Comprehensive Cancer Network, 2021, 2022c.

- (c) Tumor involvement of bone marrow
- (d) Poor performance status
- (e) Renal dysfunction (creatinine clearance less than 50 ml/min)
- (f) Liver dysfunction (bilirubin greater than 2 mg/dl)
- (g) Previous chemotherapy or radiation
- (h) Open wounds or recent surgery
- (i) Chemotherapy regimen with febrile neutropenia incidence greater than 20%
- (j) Use of specific medications (e.g., phenothiazines, diuretics, immunosuppressive drugs)
- (3) Risk for developing febrile neutropenia with hematologic malignancy (NCCN, 2022c)
  - (a) Diagnosis of acute lymphoblastic leukemia, acute myelocytic leukemia, chronic lymphocytic leukemia treated with alemtuzumab, and non-Hodgkin lymphoma, especially the T-cell subtype
  - (b) Allogeneic hematopoietic stem cell transplantation (HSCT) recipients and those with graft-versus-host disease following allogeneic HSCT
- g) Clinical manifestations of infection in patients with neutropenia (NCCN, 2022c; Taplitz et al., 2018; Territo, 2021)
  - (1) A fever greater than 100.4°F (38°C) is the most reliable indicator and often the only sign of infection in patients with neutropenia. Usually, WBCs cause the classic signs of infection (e.g., redness, edema, pus). However, extremely neutropenic patients may not be able to manifest the usual signs of infection (NCCN, 2022c; Taplitz et al., 2018; Territo, 2021).
  - (2) Common sites of infection and corresponding signs and symptoms in neutropenic patients (Camp-Sorrell, 2018; NCCN, 2022c; Territo, 2021)
    - (a) Gastrointestinal tract: fever, abdominal pain, alimentary mucositis (mucositis at any level of the digestive tract), diarrhea
    - (b) Respiratory tract: fever, cough, dyspnea on exertion, adventitious breath sounds, chest discomfort, asymmetric chest wall movement, nasal flaring
    - (c) Genitourinary tract: fever, dysuria, frequency, urgency, hematuria, cloudy urine, flank pain, perineal itching, vaginal discharge
    - (d) Head and neck: swelling, itching, eye redness or drainage, ear pain or discharge, nasal congestion or drainage, oral ulcerations, difficulty swallowing, fever
    - (e) Indwelling devices (e.g., venous access devices, ventricular peritoneal shunts): fever, erythema, pain or tenderness, edema, drainage, induration at the site
    - (f) Dermatologic and mucous membranes: erythema, tenderness, warm skin, edema (especially in axilla, mouth, sinuses, perineal, or rectal areas), rashes, itching, skin lesions, fever, draining open wounds
    - (g) Central nervous system: change in mental status, headache, seizure, vision changes, photosensitivity, fever, nausea, lethargy
    - (h) Hematologic/immunologic: decrease in diastolic blood pressure, headache, oliguria, fever, flushed appearance
  - (3) Septic shock associated with neutropenia has a high mortality rate (O'Leary, 2018). For hospitalized patients, it may be as high as 50%.

## h) ANC calculation

- (1) Use laboratory data to assess neutropenia by calculating ANC. Note that neutropenia can occur when the total WBC count is within the normal range of 4,000–10,000/mm<sup>3</sup> (Camp-Sorrell, 2018; Territo, 2021).
- (2) Calculating ANC is essential to achieving a correct assessment of neutrophil status.
- (3) To calculate ANC,  $ANC = \% \text{ neutrophils (polys + bands)} \times WBCs$ .
  - (a) Obtain complete WBC count, including differential. The differential will include mature neutrophils, referred to as segs for segmented neutrophils or PMNs/polys for polymorphonuclear neutrophils. In addition, immature neutrophils will be present; these are known as bands.
  - (b) Add the total number of mature polys and less mature neutrophil bands.
  - (c) Convert the sum from (b) to a percentage.
  - (d) Multiply total WBC count by total neutrophil percentage (polys + bands). ANC calculation example: WBCs = 1,500, polys = 30, bands = 5.
    - i. Add polys and bands:  $30 + 5 = 35$ .
    - ii. Convert sum to percentage:  $35 \div 100 = 0.35$ .
    - iii. Multiply WBC count by percentage to find ANC:  $1,500 \times 0.35 = 525/\text{mm}^3$ .

## i) Collaborative management

- (1) Nurses play an essential role in preventing infection in patients with neutropenia and cancer through evidence-based nursing practice, research, and patient education (Wilson et al., 2019).
  - (a) Hand hygiene: Proper hand hygiene is the most effective measure to prevent infection. It reduces the risk of healthcare-associated infections by decreasing the person-to-person transmission of pathogens (Camp-Sorrell, 2018; Centers for Disease Control and Prevention, 2021b; Wilson et al., 2019).
  - (b) Diet
    - i. No recent studies have linked neutropenic diets (restricting fresh fruits and vegetables) with a lower risk of infection

for neutropenic patients with cancer.

- ii. Dietary precautions regarding the omission of fresh fruits and vegetables remain unsupported (Gardner et al., 2008).
  - iii. Uncooked fruits and vegetables should be thoroughly washed (Wilson et al., 2019).
  - iv. Basic safe food handling practices should be employed, such as avoiding uncooked and undercooked meats, seafood, eggs, and unwashed fruits and vegetables (Camp-Sorrell, 2018).
- (c) Environment: Protective or strict isolation studies reveal no significant differences in documented infections, febrile episodes, or antibiotic use for patients with chemotherapy-induced neutropenia. Protective isolation has no effect on the host's endogenous flora and no impact on organisms transmitted by water or food (Camp-Sorrell, 2018).
- i. In general, patients with chemotherapy-induced neutropenia do not require specific room ventilation.
  - ii. Allogeneic HSCT recipients should reside in rooms with HEPA filtration with more than 12 air exchanges per hour. Air pressure in these rooms should be positive compared to surrounding areas, such as hallways, toilets, and anterooms (Anderson-Reitz, 2018; NCCN, 2022c; Zack, 2018).
- (d) Plants and flowers
- i. No studies are available that evaluate the potential harm of plants and flowers to patients with chemotherapy-induced neutropenia (Wilson et al., 2019).
  - ii. Because fresh or dried flowers could expose patients with cancer to *Aspergillus* and *Fusarium*, these flowers should be kept out of patient rooms (Freifeld et al., 2011).
- (e) Treatment with colony-stimulating factors (see Table 14-3)

- i. Granulocyte macrophage–colony-stimulating factor treatments include sargramostim (Genzyme, 2018).
  - ii. Granulocyte–colony-stimulating factor (G-CSF) treatments include filgrastim and pegfilgrastim (Amgen, 2021a, 2021b; Coherus BioSciences, 2021; Mylan GmbH, 2018; Pfizer, 2021a, 2021b; Sandoz, 2017, 2019; Teva Pharmaceuticals, 2019).
  - iii. NCCN (2022a) recommends using these drugs when the risk of febrile neutropenia is higher than 20%.
  - iv. The manufacturer recommends initiation of G-CSF no earlier than 24 hours following chemotherapy (Amgen, 2021a, 2021b; Coherus BioSciences, 2021; Mylan GmbH, 2018; Pfizer, 2021a, 2021b; Sandoz, 2017, 2019; Teva Pharmaceuticals, 2019).
  - v. The manufacturer of G-CSF warns that the safety of administration simultaneously with chemotherapy has not been established. The rationale is the potential sensitivity of rapidly dividing myeloid cells to cytotoxic agents (Amgen, 2021a, 2021b; Coherus BioSciences, 2021; Mylan GmbH, 2018; Pfizer, 2021a, 2021b; Sandoz, 2017, 2019; Teva Pharmaceuticals, 2019).
- (f) For patients diagnosed with small cell lung cancer and receiving platinum/etoposide or topotecan-containing regimens, administering trilaciclib prior to therapy is indicated to decrease the incidence of myelosuppression. Trilaciclib works by inhibiting CDK4/6 (cyclin-dependent kinase), which is required for HSC and progenitor cell function and to produce neutrophils, RBCs, and platelets. This transient inhibition results in the myeloprotection of HSCs and progenitor cells during the G<sub>1</sub> phase of the cell cycle.
- (g) Prevention of trauma to the patient's skin and mucous membranes is prudent based on the clinical presentation of cancer-related infections (NCCN, 2022c).
- i. Provide meticulous care for all indwelling devices.
  - ii. Prevent pressure sores and constipation (NCCN, 2022).
  - iii. Change water in pitchers, denture cups, and nebulizers daily.
  - iv. Consider the risk–benefit ratio for invasive procedures (e.g., thoracentesis, paracentesis, central vascular access device placement).
  - v. Use only an electric razor to shave unwanted hair.
  - vi. Protect skin from cuts and burns. Immediately cleanse and treat any wound that breaks the skin.
  - vii. Use a soft toothbrush for frequent oral care (minimum three to four times daily). Allow toothbrush to dry before storing.
- (h) Patient education on protective measures for neutropenic patients (Centers for Disease Control and Prevention, n.d.)
- i. Report fever, chills, and other signs and symptoms of infection at onset.
  - ii. Wash hands frequently with soap and water or an antiseptic hand rub. Hands may remain colonized with microorganisms if they are not dried properly after washing.
  - iii. Bathe daily.
  - iv. Avoid activities that may compromise skin integrity.
  - v. Wear gloves when working in the garden.
  - vi. Perform frequent oral assessment and care with a soft toothbrush.
  - vii. Cleanse the perineal area from front to back after toileting.
  - viii. Avoid exposure to pathogens or people experiencing signs and symptoms of contagious conditions.
- (i) Protective measures
- i. Do not share food utensils.

**TABLE 14-3.** Growth Factors

| Classification            | Mechanism of Action                                                           | Drug                                                            | Route | Indications                                                                                                                                                                                                   | Side Effects                                                                                                                                                                                                           | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|---------------------------|-------------------------------------------------------------------------------|-----------------------------------------------------------------|-------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Colony-stimulating factor | Stimulates erythropoiesis via the same mechanism as endogenous erythropoietin | Darbepoetin (Aranesp®)                                          | SC    | Anemia caused by concomitantly administered myelosuppressive chemotherapy in patients who, upon initiation of darbepoetin, have $\geq 2$ additional months of planned chemotherapy and hemoglobin $< 10$ g/dl | Shortness of breath, cough, low blood pressure during dialysis, abdominal pain, edema of arms and legs, hypertension, rash, urticaria, pure red cell aplasia, myalgia, infection, fatigue, diarrhea, thrombotic events | Increased risk of death and serious cardiovascular events exists when administered if hemoglobin $> 11$ g/dl.<br>Ensure adequate iron stores in patients prior to and during use.<br>The drug is not indicated for patients being treated for curative intent. An increased risk of tumor progression or recurrence exists.<br>The drug may be administered every 1 or 3 weeks. The dosing differs with these two schedules.<br>Use the lowest effective dose.<br>Do not shake vials or syringes containing the drug.<br>Store in refrigerator.<br>Do not freeze.<br>(Amgen, 2019)                                              |
|                           |                                                                               | Epoetin alfa (Epogen®, Procrit®), Epoetin alfa-epbx (Retacrit®) | SC    | Anemia caused by concomitant use of chemotherapy for $\geq 2$ months, in patients with nonmyeloid malignancies<br>Contraindicated when the goal of chemotherapy is curative                                   | Hypertension, rash, urticaria, pure red cell aplasia, myalgia, infection, fatigue, edema, diarrhea, thrombotic events                                                                                                  | Increased risk of death and serious cardiovascular events exists when administered if hemoglobin $> 11$ g/dl.<br>Ensure adequate iron stores in patients prior to and during use.<br>The drug is not indicated for patients being treated for curative intent. An increased risk of tumor progression or recurrence exists.<br>The drug may be given three times weekly or once weekly. The dosing differs with these two schedules.<br>Use the lowest effective dose.<br>Do not shake vials or syringes containing the drug.<br>Store in refrigerator.<br>Do not freeze.<br>(Amgen, 2018; Janssen Biotech, 2018; Pfizer, 2020) |

(Continued on next page)

**TABLE 14-3.** Growth Factors (*Continued*)

| Classification                                | Mechanism of Action                                            | Drug                                                                                                                         | Route  | Indications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Side Effects                                                                                                                                                                                                                                                                                              | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-----------------------------------------------|----------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|--------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Colony-stimulating factor<br>( <i>Cont.</i> ) | Regulates the production of neutrophils within the bone marrow | Filgrastim (G-CSF, Neupogen <sup>®</sup> ), filgrastim-sndz (Zarzio <sup>®</sup> ), filgrastim-aafi (Nivestym <sup>®</sup> ) | IV, SC | <p>To decrease the incidence of infection in patients with nonmyeloid malignancies who are receiving myelosuppressive cancer therapies associated with severe neutropenic fever</p> <p>To reduce the time to neutrophil recovery and duration of fever following induction or consolidation chemotherapy in patients with acute myeloid leukemia</p> <p>To reduce the duration of neutropenia and associated sequelae in patients receiving myeloablative chemotherapy prior to HSCT</p> <p>To mobilize autologous hematopoietic progenitor cells into peripheral blood for collection via leukapheresis</p> | Allergic reactions, including urticaria, rash, and facial edema; acute respiratory distress syndrome; nausea; vomiting; bone pain secondary to the rapid growth of myeloid cells in the bone marrow; fever; severe sickle cell crisis in patients with sickle cell disorder; risk of rare splenic rupture | <p>Store in refrigerator. Do not freeze. The drug may be diluted with 5% dextrose in water. Do not dilute with saline solutions. Do not shake.</p> <p>Filgrastim is not to be administered 24 hours prior to chemotherapy through 24 hours after chemotherapy completion, per the package insert.</p> <p>SC dosing continues daily for up to 14 days, until postnadir absolute neutrophil count &gt; 10,000/mm<sup>3</sup> is achieved.<br/>(Amgen, 2021b)</p> |
|                                               |                                                                | Tbo-filgrastim (Granix <sup>®</sup> )                                                                                        | SC     | To reduce the duration of severe neutropenia in patients aged 1 month or older and diagnosed with nonmyeloid malignancies being treated with anti-neoplastic agents known to cause a significant incidence of febrile neutropenia                                                                                                                                                                                                                                                                                                                                                                            | Bone pain, enlarged or ruptured spleen, dyspnea, allergic reaction, sickle cell crisis including death, glomerulonephritis, leukocytosis, aortitis, capillary leak syndrome                                                                                                                               | The drug is not recommended for simultaneous use on the same day as radiation or chemotherapy due to the potential for tumor growth stimulatory effects on malignant cells.                                                                                                                                                                                                                                                                                    |

(Continued on next page)



**TABLE 14-3.** Growth Factors (*Continued*)

| Classification                                | Mechanism of Action                                                                                                             | Drug                                                                                                                                                                                                                                                                                    | Route | Indications                                                                                                                                                          | Side Effects                                                                                                                                                                                                                                                                                                                | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|-----------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Colony-stimulating factor<br>( <i>Cont.</i> ) |                                                                                                                                 | Pegfilgrastim (Neulasta <sup>®</sup> ),<br>pegfilgrastim-apgf (Nyvepria <sup>™</sup> ),<br>pegfilgrastim-bmez (Ziextenzo <sup>™</sup> ),<br>Pegfilgrastim-cbqv (Udenyca <sup>®</sup> ),<br>Pegfilgrastim-jmdb (Fulphila <sup>™</sup> ),<br>Pegfilgrastim-apgf (Nyvepria <sup>™</sup> ). | SC    | To decrease the incidence of infection related to neutropenia in patients with nonmyeloid malignancies receiving myelosuppressive chemotherapy                       | Allergic reactions, including urticaria, rash, and facial edema; acute respiratory distress syndrome; nausea; vomiting; bone pain secondary to the rapid growth of myeloid cells in the bone marrow; fever; sickle cell crisis in patients with sickle cell disorder; injection site reaction; risk of rare splenic rupture | Pegfilgrastim is cleared by neutrophil receptor binding, with serum clearance directly related to the number of neutrophils.<br>Do not administer in the period beginning 14 days before and 24 hours after administration of cytotoxic chemotherapy.<br>Neulasta, Udenyca, Fulphila, Nyvepria, and Ziextenzo are available as a single 6 mg SC injection once per chemotherapy cycle. Neulasta is available in a sterile prefilled syringe and the sterile on-body injector to be applied on the day of treatment by a healthcare professional and designed to deliver a dose approximately 27 hours later.<br>The 6 mg fixed dose should not be administered to children or adolescents weighing less than 45 kg.<br>Store in refrigerator.<br>Do not freeze.<br>Do not shake.<br>(Amgen, 2021a; Coherus BioSciences, 2021; Mylan GmbH, 2018; Pfizer, 2021a, 2021b; Sandoz, 2019) |
| Hematopoietic stem cell mobilizer             | When combined with G-CSF, mobilizes hematopoietic stem cells to the peripheral blood where they can be collected for transplant | Plerixafor (Mozobil <sup>®</sup> )                                                                                                                                                                                                                                                      | SC    | Mobilization of hematopoietic stem cells, in combination with G-CSF, in patients with multiple myeloma or non-Hodgkin lymphoma undergoing subsequent autologous HSCT | Diarrhea, nausea, vomiting, fatigue, headache, arthralgia, dizziness, injection site reactions<br>Potential for splenic rupture, tumor cell mobilization, and embryo-fetal toxicity                                                                                                                                         | Monitor patients during and following administration for anaphylactic shock and severe hypersensitivity reactions.<br>Plerixafor is not indicated for patients with leukemia.<br>Following 4 days of once-daily G-CSF, plerixafor is administered for up to 4 consecutive days.<br>Drug is administered approximately 11 hours prior to apheresis.<br>For creatinine clearance < 50 ml/min, decrease dose by one-third to 0.16 mg/kg.                                                                                                                                                                                                                                                                                                                                                                                                                                               |

(Continued on next page)

**TABLE 14-3.** Growth Factors (*Continued*)

| Classification                                        | Mechanism of Action                                                                                                                                                                      | Drug                                                                      | Route  | Indications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Side Effects                                                                                                                                                                                                                                                                                                                          | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                           |
|-------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|--------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Hematopoietic stem cell mobilizer<br>( <i>Cont.</i> ) |                                                                                                                                                                                          | Plerixafor (Mozobil®) ( <i>Cont.</i> )                                    |        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                       | Monitor blood counts, as increased circulating leukocytes and decreased platelets have been reported.<br>(Genzyme, 2020b)                                                                                                                                                                                                                                                                                                                        |
|                                                       | Induces committed progenitor cells to divide and differentiate in the granulocyte-macrophage pathways, including neutrophils, monocytes/macrophages, and myeloid-derived dendritic cells | Sargramostim (granulocyte macrophage-colony-stimulating factor, Leukine®) | IV, SC | To shorten neutrophil recovery and reduce the incidence of infection following induction chemotherapy in patients with acute myeloid leukemia<br>To mobilize hematopoietic progenitor cells for collection via leukapheresis and to speed engraftment following autologous transplantation of progenitor cells<br>To accelerate myeloid recovery following allogeneic bone marrow or peripheral blood progenitor cell transplantation<br>For treatment in patients with delayed or failed engraftment following autologous or allogeneic HSCT | Edema, capillary leak syndrome, pleural or pericardial effusions, dyspnea, fever, abdominal pain, headache, chills, diarrhea, occasional transient supraventricular arrhythmia, bone pain secondary to the rapid growth of myeloid cells in the bone marrow<br>Infusion-related reactions, including hypersensitivity and anaphylaxis | Dilute in normal saline solution for IV use.<br>Store in refrigerator.<br>Do not freeze.<br>Do not shake.<br>Do not administer through an in-line filter.<br>Monitor complete blood count for elevated white blood cell and platelet count.<br>(Genzyme, 2018)                                                                                                                                                                                   |
| Thrombopoietic growth factor                          | Stimulates megakaryocytopoiesis and thrombopoiesis                                                                                                                                       | Oprelvekin (interleukin-11, Neumega®)                                     | SC     | To prevent severe thrombocytopenia and reduce the need for platelet transfusions in patients with nonmyeloid malignancies receiving chemotherapy with high risk of severe thrombocytopenia                                                                                                                                                                                                                                                                                                                                                    | Anaphylaxis, dilutional anemia, diarrhea, dizziness, fever, fluid retention (which can result in peripheral edema, pulmonary edema, dyspnea, capillary leak syndrome, atrial arrhythmias, and exacerbation of preexisting pulmonary effusions), headache, nausea, vomiting, insomnia, rhinitis, cough, injection site reactions       | Store in refrigerator.<br>Do not freeze.<br>Reconstitute with sterile water. Oprelvekin should be used within 3 hours of reconstitution.<br>Do not shake or freeze following reconstitution.<br>Protect from light.<br>Dosing should begin 6–24 hours after completion of chemotherapy. Discontinue when postchemotherapy platelet nadir is > 50,000/mm <sup>3</sup> and 2 days before next chemotherapy cycle.<br>(Wyeth Pharmaceuticals, 2015) |

(Continued on next page)

**TABLE 14-3.** Growth Factors (*Continued*)

| Classification         | Mechanism of Action                                                                                                                                                                 | Drug                                 | Route | Indications                                                                                                                                                                                                                                                                                                                                                                                                | Side Effects                                                                                                                                                                                                              | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|-------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Kinase inhibitor       | Transient inhibitor of cyclin-dependent kinase 4/6; hematopoietic stimulation for neutrophils, red blood cells, and platelets is dependent on cyclin-dependent kinase 4/6 activity. | Trilaciclib (Cosela™)                | IV    | To decrease the incidence of myelosuppression in adult patients with extensive-stage small cell lung cancer when administered prior to a platinum/etoposide or topotecan regimen<br>May be used before platinum/etoposide regimen with or without immune checkpoint inhibitor to decrease the incidence of anemia and red blood cell transfusions for patients with extensive-stage small cell lung cancer | Fatigue, hypocalcemia, hypokalemia, hypophosphatemia, increased aspartate aminotransferase, headache, pneumonia<br>Infusion site reactions, including phlebitis and thrombophlebitis, during infusion                     | Administer as a 30-minute infusion to be completed within 4 hours prior to the start of chemotherapy on each day chemotherapy is administered.<br>If dose is missed, discontinue chemotherapy on the day it was missed.<br>Consider resuming the drug and chemotherapy on the next scheduled chemotherapy date.<br>If the drug is discontinued, wait 96 hours from the final dose before resuming chemotherapy.                                                                                                                                                                                                                          |
| Cytokine growth factor | Binds to the human keratinocyte growth factor receptor to promote proliferation, differentiation, and migration of epithelial cells                                                 | Palifermin (human G-CSF; Kepivance®) | IV    | To decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies requiring hematopoietic stem cell support for myelotoxic therapy                                                                                                                                                                                                                                 | Common: skin toxicities (rash, edema, erythema, pruritus), fever, gastrointestinal events, respiratory complications, pain, arthralgias, dysesthesias, hypertension<br>Serious: potential for stimulation of tumor growth | Dosage is 60 mcg/kg IV bolus daily for 3 consecutive days before myelotoxic therapy (the third dose should be given 24–48 hours prior to starting myelotoxic therapy) and 3 consecutive days after myelotoxic therapy (first of these doses should be administered after, but on the same day of, hematopoietic stem cell infusion and at least 4 days after most recent dose of palifermin); a total of 6 doses is given.<br>Reconstitute with sterile water.<br>Do not shake vigorously or agitate the vial.<br>Protect from light.<br>Do not filter.<br>Discard after 1 hour at room temperature.<br>(Swedish Orphan Biovitrum, 2013) |

*Note.* Review package inserts for dosing and prescribing information.

G-CSF—granulocyte-colony-stimulating factor; HSCT—hematopoietic stem cell transplantation; IV—intravenous; SC—subcutaneous

- ii. Do not eat any food that has not been cooked or washed.
- iii. Adhere to safe food handling practices, and avoid consuming food when the safety of preparation, storage, or serving is not guaranteed.
- iv. Do not provide direct care for pets or farm animals; avoid contact with animal excreta.
- v. Refrain from direct or indirect contact with reptiles, fish, and birds.
- vi. Avoid exposure to fresh or dried plants and flowers because of the risk of *Aspergillus* infection.
- vii. Do not enter, travel through, or stay in an area of construction or renovation, where construction material or debris has been placed, or where fields have recently been plowed.
- viii. Consider vaccination for influenza and pneumonia (Centers for Disease Control and Prevention, 2021a).
- ix. Avoid contact with people who have been vaccinated with a live vaccine within the past 30 days.

(2) Management of neutropenic fever

(a) Risk factor evaluation is recommended for patients with febrile neutropenia who have not received prophylactic G-CSF.

- i. The intent is to negate poor clinical outcomes associated with febrile neutropenia and age older than 65 years, ANC less than 100 neutrophils/mm<sup>3</sup>, neutropenia expected for longer than 10 days, infection including pneumonia, or hospitalization at the time of fever.
- ii. Filgrastim, tbo-filgrastim, filgrastim-sndz, or filgrastim-aafi may be administered based on the risk for poor outcome.
- iii. Pegfilgrastim and pegfilgrastim biosimilars are not recommended for therapeutic use (NCCN, 2021, 2022b).

(b) Obtain cultures (NCCN, 2022c).

- i. Urine: Cultures are warranted when patients are symptomatic, have an indwelling urinary catheter, or if their urinalysis is abnormal.
- ii. Blood: Two blood samples should be cultured. Three options exist (NCCN, 2022).
  - One set can be obtained peripherally, and one can be obtained from a central venous catheter (preferred).
  - Both sets can be obtained peripherally.
  - Both sets can be obtained through a central venous catheter.
  - The positive predictive value of a catheter culture is less than a peripheral culture.
  - Obtaining blood cultures from the catheter and peripherally may help determine whether the catheter is the source of the bloodstream infection based on the differential time to positivity.

iii. Stool: For diarrhea, follow institutional guidelines for *Clostridium difficile* assay and enteric pathogen screen.

iv. Skin: Aspirate or biopsy skin lesions. Vesicular or ulcerated skin lesions require viral cultures.

v. Venous access device cutaneous site: Consider routine fungal/*Mycobacterium* culture if inflammation is present.

vi. Throat and nasopharynx: Sources of infection should be investigated when viral respiratory symptoms are present, especially during seasonal outbreaks.

(c) Conduct a site-specific history and physical examination to identify the source of infection (NCCN, 2022c; Taplitz et al., 2018).

- i. Assess venous access devices, skin, lungs, sinuses, mouth, pharynx, esophagus, bowel, rectum, and perivaginal and

- perirectal areas for signs and symptoms of infection.
    - ii. Obtain historical data, including comorbidities, date, last chemotherapy regimen, previous infections, recent antibiotic therapy or prophylaxis, medications, and HIV status. Explore exposure risks, including those at home with similar symptoms, pets, travel, recent blood product transfusion, or exposure to tuberculosis.
  - (d) Obtain a chest x-ray if respiratory symptoms are present.
  - (e) Once initial cultures have been obtained, administer empiric broad-spectrum antibiotics as ordered until the organism source is identified.
  - (f) Monitor blood culture reports daily and anticipate antibiotic therapy based on findings.
2. Anemia in patients with cancer
- a) Erythropoiesis: This process involves erythrocyte (RBC) production in the bone marrow (Wilson, 2018).
    - (1) The kidneys are the primary producers of erythropoietin (EPO), the growth factor that stimulates HSCs to produce RBCs.
    - (2) RBC production is regulated by oxygen levels. When oxygen levels are low, the kidney releases EPO to stimulate HSCs to produce more RBCs.
  - b) Physiology of erythrocytes (Mahdi, 2018; Turgeon, 2018)
    - (1) In the bone marrow, HSCs become erythrocytes via a series of maturation phases over approximately two days, where RBCs become smaller and more condensed.
    - (2) Beginning as a proerythroblast, the cell has a nucleus and is not condensed.
    - (3) The nucleus decreases in size as it evolves to the stages of basophilic erythroblast and then polychromatophilic erythroblast.
    - (4) In the next stage as a reticulocyte, the nucleus has been expelled from the cell, but polyribosomes remain present. Eventually, the mature erythrocyte has no nucleus or polyribosome.
  - c) RBC mass and volume: Homeostasis of erythropoiesis is a continuous process driven by oxygen levels and EPO response. The average number of circulating RBCs in adults is five million RBCs per microliter.
  - d) RBC life span
    - (1) A typical RBC has a life span of approximately 120 days in the peripheral circulation (Mahdi, 2018).
    - (2) The RBC life span, time for maturation in the bone marrow, and low turnover explain why anemia occurs later than neutropenia and thrombocytopenia following myelosuppressive therapy (Camp-Sorrell, 2018).
  - e) Pathophysiology
    - (1) Many causes for anemia exist in patients with cancer, including myelosuppressive therapy, bone marrow involvement, inadequate EPO levels due to renal insufficiency, nutritional deficits, blood loss at tumor sites, and RBC destruction (Camp-Sorrell, 2018; NCCN, 2021).
    - (2) Classification of anemia based on RBC size: Mean corpuscular volume, which reflects the size of RBCs, is used in the differential diagnosis of microcytic, normocytic, or macrocytic anemia (Braunstein, 2020).
  - f) Incidence
    - (1) Many patients (30%–90%) experience some degree of anemia associated with the diagnosis and treatment of cancer (NCCN, 2021).
      - (a) Severity may increase with comorbidities, concurrent radiation therapy, cumulative doses of cytotoxic agents, and insufficient nutritional intake.
      - (b) The incidence of anemia in patients with hematologic malignancies has been reported as three times higher than in those with solid tumors (Camp-Sorrell, 2018).
    - (2) The average time to Hgb nadir is two weeks. The cancer diagnosis, frequency of treatments, regimen, and dosing schedule contribute to the onset, severity, and duration of anemia (NCCN, 2021).
  - g) Risk factors
    - (1) Medications that suppress bone marrow function, interfere with erythrocyte development and function, or suppress EPO production
      - (a) Platinum drugs due to combined renal and bone marrow toxicity (NCCN, 2021)
      - (b) Immunotherapies (e.g., alemtuzumab) (Genzyme, 2020a)
      - (c) Pharmacologic agents (e.g., chloramphenicol, quinacrine, hydantoins) (Braunstein, 2020)

- (d) High-dose chemotherapy for HSCT
- (2) Malignancies that originate or metastasize to the bone marrow and suppress RBC precursors
- (3) Radiation therapy to areas of the skeleton involved with hematopoiesis (Camp-Sorrell, 2018; NCCN, 2021)
- (4) Acute or chronic blood loss directly related to tumor invasion
- (5) Advanced age, which places patients at risk for anemia of malignancy (NCCN, 2021, 2022b)
- (6) Poor nutrition
  - (a) Anorexia, nausea, vomiting, stomatitis, early satiety, and diarrhea may contribute to decreased oral intake and absorption of nutrients.
  - (b) Lack of calorie, protein, vitamin, and mineral intake, reflected in weight loss or weakness, compromises cellular functions, including erythrocyte production (NCCN, 2021a).
- (7) Comorbidities
  - (a) Renal insufficiency: Chemotherapy agents known to have nephrotoxic properties (e.g., cisplatin) place patients at risk because kidney function is essential for EPO production. When EPO levels are low, more hypoxia is required to stimulate EPO response (Camp-Sorrell, 2018; NCCN, 2021).
  - (b) Alcohol abuse and liver dysfunction (Braunstein, 2020)
  - (c) Cardiopulmonary disease (Braunstein, 2020; NCCN, 2021)
- (8) Female sex (Braunstein, 2020)
- h) Clinical manifestations (Braunstein, 2020)
  - (1) Cardiopulmonary
    - (a) Dyspnea and hypoxia
    - (b) Tachycardia and heart murmurs
    - (c) Orthostatic hypotension
  - (2) Integumentary
    - (a) Pallor of oral mucous membranes, conjunctivae, lips, nail beds, and palms of hands or soles of feet
    - (b) Hair loss, thinning, and early graying
    - (c) Brittle fingernails and toenails
    - (d) Cyanosis
    - (e) Hypothermia
  - (3) Neuromuscular
    - (a) Headache, dizziness
    - (b) Drowsiness, restlessness, and inability to concentrate
    - (c) Paresthesias
  - (d) Fatigue and weakness
  - (4) Decreased urine output
- i) Adverse outcomes (Gosselin, 2018)
  - (1) Because low tissue oxygenation is related to reduced sensitivity of tumors to radiation therapy and some chemotherapy, hypoxia may adversely affect treatment outcomes.
  - (2) Low oxygen levels are directly associated with fatigue and weakness and may adversely affect quality of life.
  - (3) Hypoxic tissue promotes angiogenic factors that may contribute to tumor growth.
  - (4) Postoperative mortality is increased in the presence of anemia.
  - (5) Survival times of anemic patients are shorter than those without anemia for most tumor types.
- j) Management (NCCN, 2022a)
  - (1) Fatigue is an early and frequent symptom of anemia with a significant negative impact on quality of life. Interventions should be aimed at identifying and managing fatigue.
    - (a) Encourage frequent rest periods to conserve energy.
    - (b) Use exercise when benefits outweigh risks.
    - (c) Explore complementary therapies (e.g., relaxation, massage, yoga) with the potential to minimize fatigue (NCCN, 2022a).
    - (d) Assess nutritional intake for adequate content and quantity.
    - (e) Teach patients and their family members or caregivers the importance of hydration.
  - (2) Monitor laboratory results related to anemia (see Table 14-4) and take appropriate action when abnormal (e.g., vitamin B<sub>12</sub> deficiencies, iron deficiencies).
  - (3) Interventions for hypoxia
    - (a) Provide supplemental oxygen.
    - (b) Teach energy conservation.
    - (c) Consider measures to increase Hgb (Camp-Sorrell, 2018; NCCN, 2022a).
      - i. Blood transfusions
      - ii. Erythropoiesis-stimulating agents
      - iii. Manufacturer (Amgen, 2018, 2019; Janssen Biotech, 2018; Pfizer, 2020) black box warnings are supported by eight randomized studies that each demonstrated decreased over-

**TABLE 14-4.** Laboratory Assessment of Anemia: Normal Values (Adults)

| Laboratory Test                   | Normal Value                                                                        |
|-----------------------------------|-------------------------------------------------------------------------------------|
| Coombs test (direct and indirect) | Negative                                                                            |
| Ferritin                          | Male: 20–300 ng/ml; female: 15–120 ng/ml                                            |
| Hemoglobin                        | Male: 13.5–18 g/dl; female: 12–16 g/dl                                              |
| Hematocrit                        | Male: 42%–52%; female: 37%–47%                                                      |
| Mean corpuscular volume           | 78–100 fl                                                                           |
| Mean corpuscular hemoglobin       | 27–31 pg/cell                                                                       |
| Red blood cell count              | Male: 4.7–6 million/mm <sup>3</sup> ; female: 4.2–5.4 million cells/mm <sup>3</sup> |
| Red cell distribution width       | 11.5%–14%                                                                           |
| Reticulocyte count                | 0.5%–1.85% of erythrocytes                                                          |
| Serum B <sub>12</sub>             | 190–900 pg/ml                                                                       |
| Serum erythropoietin level        | Male: 17.2 mU/ml; female: 18.8 mU/ml                                                |
| Serum folate                      | > 3.5 mcg/L                                                                         |
| Serum iron                        | Male: 75–175 mcg/dl; female: 65–165 mcg/dl                                          |
| Total iron-binding capacity       | 250–450 mcg/dl                                                                      |

Note. Based on information from Cullis, 2011; National Comprehensive Cancer Network, 2021; Weiss et al., 2019.

From "Anemia of Chronic Disease," by M. Wilks and B. Fairman, in D. Camp-Sorrell, R.A. Hawkins, and D.G. Cope (Eds.), *Clinical Manual for the Oncology Advanced Practice Nurse* (4th ed., p. 873), 2022, Oncology Nursing Society. Copyright 2022 by Oncology Nursing Society. Reprinted with permission.

all survival and locoregional control when erythropoiesis-stimulating agents were used in patients diagnosed with advanced breast, cervical, head and neck, lymphoid, and non-small cell lung cancers.

### 3. Thrombocytopenia in patients with cancer

#### a) Healthy physiology of platelets (Kuter, 2020)

- (1) The thrombocyte (platelet) precursor megakaryocyte is the largest hematopoietic cell descending from the HSC. The goal of thrombopoiesis is to produce and release mature platelets so that a healthy

amount (150,000–400,000/mm<sup>3</sup>) is circulating at any given time.

- (2) The major steps in thrombopoiesis (Machlus & Italiano, 2013)

#### (a) Two phases of megakaryocyte development

- i. The first phase takes several days marked by pronounced nuclear proliferation and an increase in cytoplasm.
- ii. During the second phase, the megakaryocytes remodel their cytoplasm into proplatelets and then into platelets.
- iii. The individual platelets are formed through fragmentation of the plasma membranes.
- iv. When the megakaryocyte completes maturation, its membrane ruptures, and the cytoplasm separates into platelets.
- v. One megakaryocyte can release thousands of platelets. The time for megakaryocytes to complete polyploidization, mature, and release platelets is approximately five days. The life span of circulating platelets is seven to eight days. There is no reserve in the bone marrow.

#### (b) Pathophysiology (Rodriguez, 2018)

- i. Thrombocytopenia after chemotherapy is evident in approximately 8–14 days and is directly related to bone marrow suppression.
- ii. Severity varies with drug, dose, and schedule.
- iii. For some agents (e.g., carmustine, carboplatin, dactinomycin, daunorubicin, lomustine, mitomycin C), it is a dose-limiting toxicity (Rodriguez, 2018).

#### b) Risk factors

- (1) Myelosuppressive chemotherapy or radiation therapy to marrow-producing skeletal sites
- (2) Immunotherapy (e.g., interferon)
- (3) Comorbidities (e.g., liver disease)
- (4) Destruction of platelets in the presence of autoimmune disease (e.g., immune thrombocytopenic purpura) or disseminated intravascular coagulation



- (5) Bone marrow infiltration of primary or metastatic malignancies
- (6) Drug therapy affecting platelet function (Camp-Sorrell, 2018; Kuter, 2020)
  - (a) Aspirin
  - (b) Nonsteroidal anti-inflammatory drugs
  - (c) Quinine and quinidine
  - (d) Thiazide diuretics (e.g., furosemide)
  - (e) Benzene and benzene derivatives
  - (f) Tricyclic antidepressants
  - (g) Antimicrobials (e.g., chloramphenicol, zidovudine)
  - (h) Heparin
- (7) Herbal agents (e.g., ginkgo, garlic, ginger, turmeric)
- c) Clinical manifestations (Rodriguez, 2018)
  - (1) Cardiopulmonary
    - (a) Adverse changes in peripheral pulses, tachycardia, hypotension, and orthopnea
    - (b) Dyspnea, tachypnea, adventitious breath sounds, and hemoptysis
  - (2) Head and neck
    - (a) Petechiae of oral or nasal membranes
    - (b) Epistaxis
    - (c) Periorbital edema, subconjunctival hemorrhage, eye pain, and blurred or double vision
  - (3) Integumentary system
    - (a) Petechiae, bruising, pallor, or acrocyanosis anywhere on the skin or mucous membranes
    - (b) Bleeding from surgery, devices, or wound sites
  - (4) Neurologic
    - (a) Change in mental status, confusion, restlessness, or lethargy
    - (b) Widening pulse pressure, an abnormal change in pupil size, diminished reflexes, or loss of motor strength or coordination
    - (c) Headache and seizures
  - (5) Gastrointestinal
    - (a) Abdominal pain or distension
    - (b) Rectal bleeding, tarry stools, and hematemesis
    - (c) Enlarged and palpable spleen
  - (6) Genitourinary
    - (a) Menorrhagia
    - (b) Hematuria, dysuria, and low urine output
- d) Management
  - (1) Monitor laboratory findings and take appropriate action.
    - (a) Obtain platelet count, prothrombin time, partial thromboplastin time, Hgb, hematocrit, D-dimer, fibrinogen, and fibrin.
    - (b) Test stool, urine, and emesis for occult blood.
  - (2) Maintain a safe environment.
    - (a) Instruct patients to avoid activities that may cause injury.
    - (b) Assess the home environment and use nonskid rugs, nightlights, and ambulatory assistive devices to prevent falls.
  - (3) Educate patients and families on ways to maintain skin integrity through the following (Rodriguez, 2018).
    - (a) Using a soft toothbrush
    - (b) Blowing nose gently
    - (c) Using an electric razor versus a straight razor
    - (d) Using an emery board versus a metal nail file
    - (e) Using water-soluble lubricants for sexual intercourse
    - (f) Avoiding any sexual activity that may compromise skin or mucous membrane integrity
    - (g) Avoiding the use of tampons
    - (h) Using laxatives or stool softeners to avoid constipation
    - (i) Refraining from using mechanical, oral irrigation, or aggressive dental flossing
    - (j) Avoiding dental and other invasive procedures
  - (4) Medications and treatments (Rodriguez, 2018)
    - (a) Administer platelet transfusions.
    - (b) Consider administering interleukin-11 (Wyeth Pharmaceuticals, 2015).

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## CHAPTER 15

# Gastrointestinal and Mucosal Toxicities

### A. Nausea and vomiting

1. Overview: Up to 80% of patients with cancer may experience nausea and vomiting, and these symptoms can be the most distressing and feared side effects of cancer treatment (Lee et al., 2019; National Cancer Institute [NCI], 2021b).

- a) Adherence to antiemetic guidelines has been shown to decrease the incidence of chemotherapy-induced nausea and vomiting (CINV) in patients receiving highly or moderately emetogenic chemotherapy (Abunahlah et al., 2016; Gilmore et al., 2014; Patil et al., 2017).

- b) Continued advances in the scientific understanding of the pathophysiology of CINV have produced increasingly effective antiemetic agents and combination regimens. Prevention of acute emesis associated with highly emetogenic chemotherapy can be achieved in 50%–75% of patients. In those receiving moderately emetogenic chemotherapy, successful prevention of acute emesis improves to 75%–90% of patients (Escobar et al., 2015; Navari et al., 2016; Wickham, 2012).

- c) Despite these advances in acute emesis control, higher percentages of patients continue to experience suboptimal control of delayed CINV symptoms, most notably nausea, which is significantly underestimated by clinicians (Naito et al., 2020; Vidall et al., 2015).

- d) Given the prominent negative impact of CINV on patient quality of life, oncology nurses must be vigilant and proactive when assessing for and managing CINV (Sommariva et al., 2016).

2. Definitions

- a) Nausea is an unpleasant subjective awareness of the need to vomit; the experience is described as a wavelike feeling occurring in the stomach or back of the throat; it typically precedes vomiting (Camp-Sorrell, 2018; NCI, 2021b).

- b) Retching is a rhythmic contraction involving the esophagus, diaphragm, and abdominal muscles to

eject stomach contents; this is commonly referred to as “dry heaves” (NCI, 2021b).

- c) Vomiting is the forceful expulsion of gastric contents through the mouth (NCI, 2021b).

3. Pathophysiology

- a) Nausea, retching, and vomiting are independent phenomena that can occur sequentially or as separate entities. Progress continues in understanding the complex neurophysiologic structures in the central and peripheral nervous systems and the gastrointestinal (GI) tract that underly CINV (NCI, 2021b).

- b) Nausea is mediated through the autonomic nervous system; however, its subjective nature results in less-precise insight into its mechanisms (NCI, 2021b).

- c) Vomiting results from the stimulation of a complex process that involves the activation of various peripheral and central pathways and neurotransmitter receptors (see Figures 15-1 and 15-2).

- d) The emetic reflex is thought to be influenced by three separate areas of the brain stem: the central pattern generator (commonly referred to as the vomiting center [VC]) and two areas in the dorsal brain stem called the nucleus tractus solitarius and area postrema, which are commonly referred to as the chemotherapy trigger zone (CTZ) (Hesketh, 2022a).

- e) The VC is a cluster of neurons located in the medulla. Stimulation of the VC results in efferent impulses from the central nervous system to the salivation center, cranial nerves, respiratory center, and abdominal muscles. This leads to the initiation of emesis (National Comprehensive Cancer Network [NCCN], 2022b; Navari & Aapro, 2016). In other words, the VC is the final common pathway for emesis; it serves as the control and integration center for the numerous inputs and stimuli from various sources and sends signals to different organs and tissues, resulting in vomiting (Tipton, 2014).

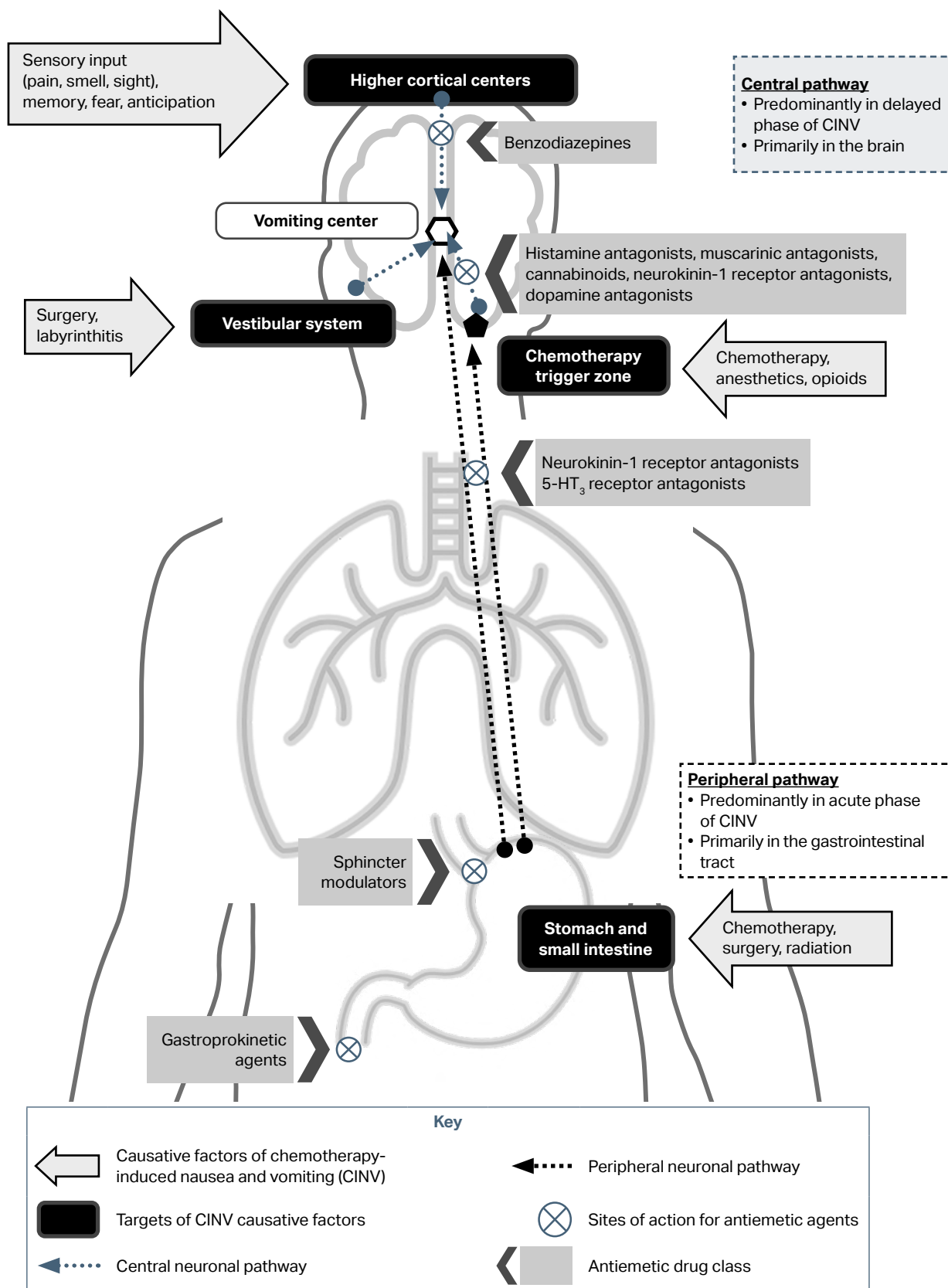
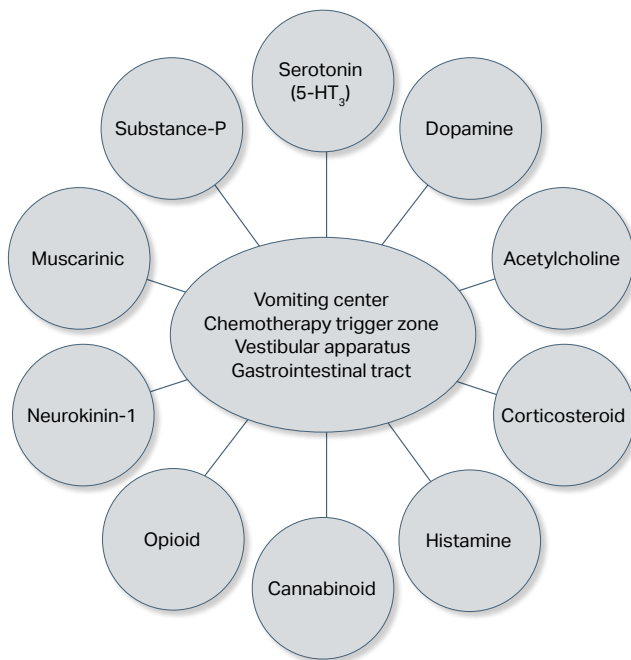
**FIGURE 15-1.** Mechanisms of Emesis

**FIGURE 15-2.** Neuroreceptors

Note. Based on information from National Comprehensive Cancer Network, 2022b.

f) The VC may be stimulated through peripheral or central pathways.

(1) Vagal afferents: GI and pharyngeal

(a) The GI vagal afferent is thought to be the primary cause of acute chemotherapy-induced vomiting (Hesketh, 2008).

(b) Chemotherapy stimulates enterochromaffin cells in the GI tract, causing them to release serotonin (5-hydroxytryptamine-3 [5-HT<sub>3</sub>]) (Hesketh, 2008).

(c) Serotonin release causes the activation of the vagus nerve, which stimulates vomiting through the VC (Hesketh, 2008; Navari & Aapro, 2016).

(d) 5-HT<sub>3</sub> receptors along the vagus nerve may also be involved in acute nausea and vomiting related to abdominal distension, radiation to the abdomen or chest, and pharyngeal irritation (Tipton, 2014).

(e) Additional receptors involved in this process may include neurokinin-1 (NK<sub>1</sub>) and cholecystokinin-1 (Hesketh, 2008).

(f) This peripheral nervous system pathway is primarily associated with acute emesis occurring within 24

hours of chemotherapy (Hesketh, 2022a).

(2) CTZ

(a) The CTZ, formed by the nucleus tractus solitarius and area postrema, is located at the caudal end of the fourth ventricle of the brain (Hesketh, 2008, 2022a; Navari & Aapro, 2016).

(b) The CTZ lies outside of the blood-brain barrier. As a result, the CTZ may be stimulated by emetogens in the blood or cerebrospinal fluid (Hesketh, 2022a).

(c) The CTZ appears to be a prominent source of afferent input to the VC and is an important site for neurotransmitter receptors involved in the vomiting response, including 5-HT<sub>3</sub>, NK<sub>1</sub>, muscarinic (M<sub>1</sub>), dopamine (D<sub>2</sub>), and histamine (H<sub>1</sub>) receptors (Hesketh, 2022a).

(d) Opioids, dopaminergic agonists, chemotherapy, and toxins may stimulate the CTZ and result in vomiting (Hesketh, 2008).

(e) This central nervous system pathway is primarily associated with delayed CINV, occurring more than 24 hours after chemotherapy (Hesketh, 2022a).

(3) Higher cortical centers: Nausea and vomiting may result from anxiety, memory, fear, pain, or a conditioned response to sights or smells; this is predominantly displayed as anticipatory nausea and vomiting (Hesketh, 2022a).

(4) Vestibular apparatus

(a) Labyrinthitis and motion sickness may result in nausea and vomiting (Tipton, 2014).

(b) Surgery can also induce vomiting through stimulation of the vestibular system.

(5) Other potential causes of nausea and vomiting (NCCN, 2022b)

(a) Brain metastases

(b) Side effects of other medications

(c) Excessive secretions

(d) Gastroparesis

(e) Electrolyte imbalance

(f) Uremia

(g) Anxiety

(h) Vestibular dysfunction

(i) Malignant ascites



- (j) Partial or complete bowel obstruction
  - (k) Cannabinoid hyperemesis syndrome
  - (l) Rapid opioid withdrawal
  - (m) Pancreatitis
4. Risk factors and classification of CINV
- a) Most patients are at some degree of risk for experiencing CINV. However, patient-specific factors related to the disease site, chemotherapy agents, and personal history can influence the onset, severity, and duration of symptoms (Hesketh, 2022a; NCI, 2021b).
  - b) Patient-related risk factors (Camp-Sorrell, 2018; Molassiotis et al., 2016; NCCN, 2022b; NCI, 2021b)
    - (1) Anxiety prior to the chemotherapy cycle
    - (2) History of poorly controlled CINV with previous encounters
    - (3) Expectancy of experiencing CINV after treatment
    - (4) Young or middle-aged patients (e.g., younger than age 50 years)
    - (5) Female sex
    - (6) Alcohol use: Patients who have a history of low or no alcohol consumption have more nausea and vomiting than patients with a history of high alcohol consumption.
    - (7) Susceptibility to motion sickness
    - (8) History of pregnancy-induced nausea and vomiting (e.g., morning sickness)
  - c) Acute-onset CINV may occur within a few minutes of chemotherapy administration. It typically peaks after five to six hours and resolves within 24 hours (NCCN, 2022b).
    - (1) Incidence: Acute CINV is predominantly related to the drug class, dose level, frequency of administration, and emetogenic potential of the antineoplastic agent or combination regimen (NCI, 2021b).
      - (a) Hesketh et al. (1997) originally developed the classification of chemotherapy agents based on the risk of acute emetogenicity without antiemetic prophylaxis; this work also produced an algorithm to define the emetogenic risk of multiagent regimens and served as the framework for future guideline development.
      - (b) Grunberg et al. (2005) further refined the classification into four categories for the emetogenic potential of IV chemotherapy. Current treatment guidelines published by NCCN, the American Society of Clinical Oncology (ASCO), and the Multinational Association of Supportive Care in Cancer/European Society for Medical Oncology (MASCC/ESMO) are based on these categories (Hesketh et al., 2020; NCCN, 2022b; Roila et al., 2016).
        - i. High: Emesis occurs in greater than 90% of patients.
        - ii. Moderate: Emesis occurs in 30%–90% of patients.
        - iii. Low: Emesis occurs in 10%–30% of patients.
        - iv. Minimal: Emesis occurs in fewer than 10% of patients.
      - (c) The routine use of antiemetic prophylaxis also affects the observed incidence of acute CINV (Gilmore et al., 2014).
  - (2) Prevention of acute CINV (NCCN, 2022b)
    - (a) Prophylactic medications should be administered before chemotherapy.
    - (b) If the patient is receiving chemotherapy from multiple emetogenic risk categories, prophylactic antiemetic therapy should be based on the highest emetogenic risk medication (Hesketh et al., 2020; NCCN, 2022b).
  - d) Delayed-onset CINV occurs more than 24 hours after chemotherapy administration and may last for several days (NCCN, 2022b; NCI, 2021b).
    - (1) Incidence: Delayed-onset CINV occurs commonly with highly emetogenic chemotherapy, single-agent administration, and regimens that include carboplatin, cisplatin, cyclophosphamide, or anthracyclines.
    - (2) It is more common in patients who have experienced acute emesis.
    - (3) For multiday treatments, the time frame of delayed emesis may depend on the chemotherapy agents included in the regimen and the emetogenic potential of agents administered on the final day of treatment.
  - e) Anticipatory CINV occurs in the days or hours leading up to chemotherapy administration. It is likely a conditioned response, and therefore, occurs after a previous experience with CINV (NCCN, 2022b).
    - (1) Incidence: Anticipatory CINV occurs in 18%–57% of patients, with nausea being more common than vomiting (NCCN, 2022b).

- (2) It may be triggered by a particular smell, taste, sight, or sound experienced in the treatment environment (NCI, 2021b).
  - (3) To minimize the risk of anticipatory CINV, effective and proactive antiemetic control and prevention of acute and delayed CINV are essential.
  - f) Breakthrough CINV occurs following chemotherapy administration, despite guideline-driven prophylactic antiemetic treatment, and may require rescue antiemetics (Navari, 2015).
  - g) Refractory CINV occurs when guideline-driven antiemetic prophylaxis has not been effective in the previous cycle and continues to be ineffective in a subsequent cycle (Navari, 2015).
5. Assessment: Identify the potential patient-related risks and physiologic causes of nausea and vomiting, classify the type of nausea and vomiting, and determine the level of emetogenicity of the chemotherapy agents prescribed (see Figures 15-3 and 15-4). See Table 15-1 for NCI's toxicity criteria and grading scale for nausea and vomiting.

a) Chemotherapy (NCCN, 2022b)

- (1) Evaluate the emetogenic potential of all prescribed chemotherapy agents, including oral and IV formulations, and verify that the patient has appropriate antiemetics premedications ordered as part of their treatment regimen.
- (2) Confirm that the patient has been prescribed and has successfully obtained antiemetic prescriptions through their retail pharmacy for delayed and breakthrough CINV at home. Evaluate the need for financial assistance related to prescription coverage and refer to appropriate resources.

b) Immunotherapy

- (1) Patients receiving immunotherapy agents may experience nausea and vomiting as part of a flu-like syndrome.
- (2) Monoclonal antibodies may be associated with acute nausea and vomiting during the infusion or hypersensitivity reaction.

**FIGURE 15-3.** Emetogenic Potential of Intravenous Antineoplastic Drugs

| Medications With High Incidence (90%–100%)                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                       |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>AC combination (doxorubicin or epirubicin + cyclophosphamide)<sup>a</sup></li> <li>Carboplatin (AUC ≥ 4 mg/ml × min)<sup>b</sup></li> </ul>                                                                                                                                                                                                                                                                                                                 | <ul style="list-style-type: none"> <li>Carmustine (&gt; 250 mg/m<sup>2</sup>)</li> <li>Cisplatin</li> <li>Cyclophosphamide (≥ 1,500 mg/m<sup>2</sup>)</li> <li>Dacarbazine</li> </ul>                                                                                                                                                                                                                                                         | <ul style="list-style-type: none"> <li>Doxorubicin (≥ 60 mg/m<sup>2</sup>)<sup>b</sup></li> <li>Epirubicin (&gt; 90 mg/m<sup>2</sup>)<sup>b</sup></li> <li>Fam-trastuzumab deruxtecan-nxki</li> <li>Ifosfamide (≥ 2 g/m<sup>2</sup> per dose)<sup>b</sup></li> </ul>                                                                                                                  | <ul style="list-style-type: none"> <li>Mechlorethamine</li> <li>Melphalan (≥ 140 mg/m<sup>2</sup>)</li> <li>Sacituzumab govitecan-hziy</li> <li>Streptozocin</li> </ul>                                                                               |
| Medications With Moderate Incidence (30%–90%)                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                       |
| <ul style="list-style-type: none"> <li>Aldesleukin (&gt; 12–15 MIU/m<sup>2</sup>)</li> <li>Amifostine (&gt; 300 mg/m<sup>2</sup>)</li> <li>Azacitidine</li> <li>Bendamustine</li> <li>Busulfan<sup>b</sup></li> <li>Carboplatin (AUC &lt; 4 mg/ml × min)</li> <li>Carmustine (≤ 250 mg/m<sup>2</sup>)<sup>b</sup></li> </ul>                                                                                                                                                                       | <ul style="list-style-type: none"> <li>Clofarabine</li> <li>Cyclophosphamide (&lt; 1,500 mg/m<sup>2</sup>)</li> <li>Cytarabine (&gt; 200 mg/m<sup>2</sup>)<sup>b</sup></li> <li>Dactinomycin</li> <li>Daunorubicin</li> <li>Daunorubicin and cytarabine liposome</li> </ul>                                                                                                                                                                   | <ul style="list-style-type: none"> <li>Dinutuximab</li> <li>Doxorubicin (&lt; 60 mg/m<sup>2</sup>)</li> <li>Epirubicin (≤ 90 mg/m<sup>2</sup>)</li> <li>Idarubicin</li> <li>Ifosfamide (&lt; 2 g/m<sup>2</sup> per dose)</li> <li>Irinotecan</li> <li>Irinotecan liposomal</li> </ul>                                                                                                 | <ul style="list-style-type: none"> <li>Lurbinectedin</li> <li>Melphalan (&lt; 140 mg/m<sup>2</sup>)<sup>b</sup></li> <li>Methotrexate (≥ 250 mg/m<sup>2</sup>)<sup>b</sup></li> <li>Oxaliplatin</li> <li>Temozolomide</li> <li>Trabectedin</li> </ul> |
| Medications With Low Incidence (10%–30%)                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                       |
| <ul style="list-style-type: none"> <li>Ado-trastuzumab emtansine</li> <li>Aldesleukin (≤ 12 MIU/m<sup>2</sup>)</li> <li>Amifostine (≤ 300 mg/m<sup>2</sup>)</li> <li>Arsenic trioxide<sup>b</sup></li> <li>Axicabtagene ciloleucel</li> <li>Belinostat</li> <li>Brentuximab</li> <li>Brentuximab vedotin</li> <li>Brexucabtagene autoleucel</li> <li>Cabazitaxel</li> <li>Carfilzomib</li> <li>Copanlisib</li> <li>Cytarabine (100–200 mg/m<sup>2</sup>)<sup>b</sup></li> <li>Docetaxel</li> </ul> | <ul style="list-style-type: none"> <li>Doxorubicin (liposomal)</li> <li>Enfortumab vedotin-ejfv</li> <li>Eribulin</li> <li>Etoposide</li> <li>5-Fluorouracil</li> <li>Floxuridine</li> <li>Gemcitabine</li> <li>Gemtuzumab ozogamicin</li> <li>Inotuzumab ozogamicin</li> <li>Isatuximab-irfc</li> <li>Ixabepilone</li> <li>Methotrexate (&gt; 50 mg/m<sup>2</sup> but &lt; 250 mg/m<sup>2</sup>)<sup>b</sup></li> <li>Mitomycin C</li> </ul> | <ul style="list-style-type: none"> <li>Mitoxantrone</li> <li>Mitoxantrone pyelocalyceal solution</li> <li>Mogamulizumab</li> <li>Moxetumomab</li> <li>Necitumumab</li> <li>Olaratumab</li> <li>Omacetaxine</li> <li>Paclitaxel</li> <li>Paclitaxel, albumin bound</li> <li>Pemetrexed</li> <li>Pentostatin</li> <li>Polatuzumab vedotinb</li> <li>Pralatrexate<sup>b</sup></li> </ul> | <ul style="list-style-type: none"> <li>Romidepsinb</li> <li>Tafasitamab-cxix</li> <li>Tagraxofusp</li> <li>Talimogene laherparepvec</li> <li>Thiotepa<sup>b</sup></li> <li>Tisagenlecleucel</li> <li>Topotecan</li> <li>Ziv-aflibercept</li> </ul>    |

(Continued on next page)

**FIGURE 15-3.** Emetogenic Potential of Intravenous Antineoplastic Drugs (*Continued*)

| Medications With Minimal Incidence (< 10%)                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                            |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>• Alemtuzumab<sup>b</sup></li> <li>• Asparaginase</li> <li>• Atezolizumab</li> <li>• Avelumab</li> <li>• Bevacizumab</li> <li>• Bleomycin</li> <li>• Blinatumomab<sup>b</sup></li> <li>• Bortezomib<sup>b</sup></li> <li>• Cemiplimab</li> <li>• Cetuximab<sup>b</sup></li> <li>• Cladribine</li> <li>• (2-chlorodeoxyadenosine)</li> <li>• Cytarabine (&lt; 100 mg/m<sup>2</sup>)<sup>b</sup></li> </ul> | <ul style="list-style-type: none"> <li>• Daratumumab</li> <li>• Daratumumab/hyaluronidase-fihj</li> <li>• Decitabine</li> <li>• Denileukin diftitox</li> <li>• Dexrazoxane</li> <li>• Durvalumab</li> <li>• Elotuzumab<sup>b</sup></li> <li>• Emapalumab</li> <li>• Fludarabine</li> <li>• Ipilimumab<sup>b</sup></li> <li>• Luspatercept-aamt</li> <li>• Methotrexate (&lt; 50 mg/m<sup>2</sup>)<sup>b</sup></li> </ul> | <ul style="list-style-type: none"> <li>• Nelarabine</li> <li>• Nivolumab</li> <li>• Obinutuzumab</li> <li>• Ofatumumab</li> <li>• Panitumumab<sup>b</sup></li> <li>• PEG-asparaginase</li> <li>• Pembrolizumab</li> <li>• Pertuzumab<sup>b</sup></li> <li>• Pertuzumab/trastuzumab/hyaluronidase-zzxf</li> <li>• Ramucirumab</li> <li>• Rituximab</li> </ul> | <ul style="list-style-type: none"> <li>• Rituximab/hyaluronidase human (subcutaneous injection)</li> <li>• Siltuximab</li> <li>• Temsirolimus<sup>b</sup></li> <li>• Trastuzumab</li> <li>• Trastuzumab/hyaluronidase<sup>b</sup></li> <li>• Valrubicin</li> <li>• Vinblastine</li> <li>• Vincristine</li> <li>• Vincristine (liposomal)</li> <li>• Vinorelbine</li> </ul> |

<sup>a</sup> Any regimen that includes an anthracycline and cyclophosphamide (e.g., regimen consisting of cyclophosphamide, doxorubicin, vincristine, and prednisone)

<sup>b</sup> Discrepancies in categorization noted in the references

AC—anthracycline plus cyclophosphamide; AUC—area under the plasma concentration versus-time curve; MIU—million international units

Note. Based on information from Grunberg et al., 2011; National Comprehensive Cancer Network, 2022b; Roila et al., 2016.

- (3) Cytokine release syndrome, a possible toxicity related to chimeric antigen receptor (CAR) T cells, monoclonal antibodies, and other immunotherapies, may result in nausea and vomiting (Bonifant et al., 2016; Kroschinsky et al., 2017).
- (4) Biosimilars are expected to have the same emetic risk as to the originator product unless expressly noted otherwise (NCCN, 2022b).
- c) Targeted therapy (Navari & Aapro, 2016; Roila et al., 2016)
  - (1) New targeted therapies have varying doses and combinations and extended schedules that may include daily oral use.
  - (2) Because of the lack of prospective trials regarding nausea and vomiting related to targeted therapies given in the absence of antiemetic therapy, evidence regarding emetogenicity and appropriate antiemetic therapy for these medications is limited.
  - (3) The incidence and severity of nausea and vomiting with targeted therapies are not well studied.
  - (4) As increasing numbers of oral targeted therapies are approved, it is important to review antiemetic guidelines for appropriate management recommendations.
- d) Radiation therapy can produce or compound nausea and vomiting when administered locally near the upper abdomen, as total body irradiation (TBI), or when combined with chemotherapy as sensitization (NCCN, 2022b).
- e) Physical causes (NCCN, 2022b)
  - (1) Tumor obstruction
  - (2) Gastroparesis
  - (3) Constipation
  - (4) Increased intracranial pressure
  - (5) Brain metastasis
  - (6) Vestibular dysfunction
  - (7) Uncontrolled pain
  - (8) Fluid volume status
  - (9) Pancreatitis
- f) Metabolic causes
  - (1) Hypercalcemia
  - (2) Hyponatremia
  - (3) Hyperglycemia
  - (4) Uremia
  - (5) Increased creatinine
- g) Other medications or agents (e.g., opioids, antibiotics, cannabis)
  - (1) Rapid opioid withdrawal
  - (2) Cannabinoid hyperemesis syndrome
- h) Psychological causes
  - (1) Anxiety
  - (2) Fear
  - (3) Emotional distress
6. Potential complications of nausea and vomiting (Camp-Sorrell, 2018; NCI, 2022b; Tipton, 2014)
  - a) Discomfort
  - b) Treatment delay or withdrawal from treatment
  - c) Diminished quality of life (e.g., impaired mobility, fatigue)
  - d) Dehydration
  - e) Metabolic disturbances
  - f) Anorexia, weight loss, and nutritional depletion

- g) Physical and mental deterioration
  - h) Increased intracranial pressure
  - i) Aspiration
  - j) Esophageal tears
  - k) Wound dehiscence
  - l) Decreased ability to perform self-care
  - m) Costs associated with treatment
  - n) Family and caregiver strain
  - o) Lost productivity and missed work
7. Collaborative management: pharmacologic interventions
- a) Antiemetic therapy aims to prevent nausea and vomiting (NCCN, 2022b).
    - (1) Consider the level of emetogenicity based on the medication, route of administration, and dose administered. Choose the prophylactic antiemetic regimen based on the drug with the highest emetogenicity. Consider patient-specific risk factors (Hesketh et al., 2020; Roila et al., 2016).
    - (2) Patients receiving multiday regimens must be assessed for acute and delayed

CINV based on the emetogenicity of the individual drugs on each given day and the timing of administration in the drug sequence. Overlap of acute and delayed CINV can occur (NCCN, 2022b).

- (3) Patient response to pharmacologic interventions for nausea and vomiting requires frequent assessment, with treatment modification as appropriate (NCCN, 2022b).
- (4) Corticosteroids are not recommended as antiemetic prophylaxis or treatment with cellular therapies, such as CAR T-cell therapy, due to the risk of decreased persistence of the population postinfusion. They should be avoided three to five days prior to and 90 days after CAR T-cell infusion (NCCN, 2022b).
- (5) It is recommended that checkpoint inhibitors, including programmed cell death protein 1 (PD-1), programmed cell death-ligand 1 (PD-L1), and cytotoxic

**FIGURE 15-4.** Emetogenic Potential of Oral Antineoplastic Drugs

| Medications With Moderate to High Incidence (≥ 30%)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>• Altretamine</li> <li>• Avapritinib</li> <li>• Azacytidine</li> <li>• Binimetinib</li> <li>• Bosutinib (&gt; 400 mg daily)</li> <li>• Busulfan (≥ 4 mg/dl)</li> <li>• Capmatinib</li> <li>• Ceritinib</li> </ul>                                                                                                                                                                                                                                                                                                                                         | <ul style="list-style-type: none"> <li>• Crizotinib</li> <li>• Cyclophosphamide (≥ 100 mg/m<sup>2</sup> daily)</li> <li>• Dabrafenib<sup>a</sup></li> <li>• Enasidenib</li> <li>• Encorafenib<sup>a</sup></li> <li>• Estramustine<sup>a</sup></li> </ul>                                                                                                                                                                                                                                                                          | <ul style="list-style-type: none"> <li>• Etoposide<sup>a</sup></li> <li>• Fedratinib</li> <li>• Imatinib (&gt; 400 mg daily)</li> <li>• Lenvatinib (&gt; 12 mg daily)</li> <li>• Lomustine (single day)</li> <li>• Midostaurin</li> <li>• Mitotane</li> </ul>                                                                                                                                                                                                                                                               | <ul style="list-style-type: none"> <li>• Niraparib</li> <li>• Olaparib<sup>a</sup></li> <li>• Procarbazine</li> <li>• Rucaparib</li> <li>• Selinexor</li> <li>• Temozolomide (&gt; 75 mg/m<sup>2</sup> daily)<sup>a</sup></li> </ul>                                                                                                                                                                                                                                                                                          |
| Medications With Minimal to Low Incidence (< 30%)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <ul style="list-style-type: none"> <li>• Abemaciclib<sup>a</sup></li> <li>• Acalabrutinib</li> <li>• Afatinib</li> <li>• Alectinib</li> <li>• Apelisisib</li> <li>• Axitinib</li> <li>• Bexarotene</li> <li>• Bosutinib (≤ 400 mg daily)</li> <li>• Brigatinib</li> <li>• Busulfan (&lt; 4 mg daily)</li> <li>• Cabozantinib<sup>a</sup></li> <li>• Capecitabine</li> <li>• Chlorambucil</li> <li>• Cobimetinib</li> <li>• Cyclophosphamide (&lt; 100 mg/m<sup>2</sup> daily)</li> <li>• Dacomitinib</li> <li>• Dasatinib</li> <li>• Decitabine and cedazuridine</li> <li>• Duvelisib</li> </ul> | <ul style="list-style-type: none"> <li>• Entrectinib</li> <li>• Erdafitinib</li> <li>• Erlotinib</li> <li>• Everolimus</li> <li>• Fludarabine</li> <li>• Gefitinib</li> <li>• Gilteritinib</li> <li>• Glasdegib</li> <li>• Hydroxyurea</li> <li>• Ibrutinib</li> <li>• Idelalisib</li> <li>• Imatinib (≤ 400 mg daily)</li> <li>• Ivosidenib</li> <li>• Ixazomib</li> <li>• Lapatinib</li> <li>• Larotrectinib</li> <li>• Lenalidomide</li> <li>• Levatinib (≤ 12 mg daily)</li> <li>• Lorlatinib</li> <li>• Melphalan</li> </ul> | <ul style="list-style-type: none"> <li>• Mercaptopurine</li> <li>• Methotrexate</li> <li>• Neratinib</li> <li>• Nilotinib</li> <li>• Osimertinib</li> <li>• Palbociclib</li> <li>• Panobinostat</li> <li>• Pazopanib</li> <li>• Pemigatinib</li> <li>• Pexidartinib</li> <li>• Pomalidomide</li> <li>• Ponatinib</li> <li>• Pralsetinib</li> <li>• Regorafenib</li> <li>• Ribociclib<sup>a</sup></li> <li>• Ripretinib</li> <li>• Ruxolitinib</li> <li>• Selpercatinib</li> <li>• Sonidegib</li> <li>• Sorafenib</li> </ul> | <ul style="list-style-type: none"> <li>• Sunitinib</li> <li>• Talazoparib tosylate</li> <li>• Tazemetostat</li> <li>• Tegafur-uracil</li> <li>• Temozolomide (≤ 75 mg/m<sup>2</sup> daily)</li> <li>• Thalidomide</li> <li>• Thioguanine</li> <li>• Topotecan</li> <li>• Trametinib</li> <li>• Tretinoin</li> <li>• Trifluridine/tipiracil<sup>a</sup></li> <li>• Tucatinib</li> <li>• Vandetanib</li> <li>• Vemurafenib</li> <li>• Venetoclax</li> <li>• Vismodegib</li> <li>• Vorinostat</li> <li>• Zanubrutinib</li> </ul> |

<sup>a</sup> Discrepancies noted in the references

Note. Based on information from Grunberg et al., 2011; National Comprehensive Cancer Network, 2022b; Roila et al., 2016.

**TABLE 15-1.** Common Terminology Criteria for Adverse Events Grading for Nausea and Vomiting

| Adverse Event | Grade                                                |                                                                                     |                                                                                          |                               |       |
|---------------|------------------------------------------------------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|-------------------------------|-------|
|               | 1                                                    | 2                                                                                   | 3                                                                                        | 4                             | 5     |
| Nausea        | Loss of appetite without alteration in eating habits | Oral intake decreased without significant weight loss, dehydration, or malnutrition | Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated | –                             | –     |
| Vomiting      | Intervention not indicated                           | Outpatient IV hydration; medical intervention indicated                             | Tube feeding, TPN, or hospitalization indicated                                          | Life-threatening consequences | Death |

TPN—total parenteral nutrition

Note. From *Common Terminology Criteria for Adverse Events* [v5.0], by National Cancer Institute Cancer Therapy Evaluation Program, 2017 ([https://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/docs/CTCAE\\_v5\\_Quick\\_Reference\\_5x7.pdf](https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf)). In the public domain.

T-lymphocyte antigen 4 (CTLA-4), not be administered with concurrent, prolonged therapeutic steroids due to concerns of potential adverse effects on drug efficacy through dampening of the immune response (Hesketh et al., 2020).

(a) When checkpoint inhibitors are administered as single-agent or combination therapy, the emetogenic risk is minimal, and no CINV prophylaxis is required (NCCN, 2022b).

(b) Checkpoint inhibitors are increasingly combined with chemotherapy agents of various emetogenic risk categories. Insufficient evidence exists to recommend omitting dexamethasone from antiemetic prophylaxis following current antiemesis guidelines for combination regimens that include checkpoint inhibitors, given the short duration of steroid administration relative to treatment cycle length (Hesketh, 2022b; Hesketh et al., 2020).

(6) Dexamethasone-sparing antiemetic prophylaxis regimens using alternate, less frequent, or individualized dosing of dexamethasone may be appropriate for patients receiving moderately emetogenic chemotherapy, non-cisplatin highly emetogenic chemotherapy, or combination anthracycline and cyclophosphamide regimens who are intolerant of corticosteroid adverse effects (i.e., insomnia, GI upset, agitation, increased appetite, or weight gain) or have complicating comorbidities (e.g., diabetes mellitus) (Lee et al., 2019; NCCN, 2022b; Okada et al., 2019).

b) Prevention and management of anticipatory CINV

(1) With anticipatory CINV being a learned behavioral response, the best means of prevention is to provide the most effective control of acute and delayed CINV in the initial treatment cycles (Roila et al., 2016).

(2) Benzodiazepines may reduce the occurrence of anticipatory CINV. They should be administered beginning the night before treatment and may be repeated one to two hours before chemotherapy (NCCN, 2022b; Roila et al., 2016).

c) Prevention and management of acute and delayed CINV related to IV antineoplastic administration

(1) ASCO, MASCC/ESMO, and NCCN have published antiemetic guidelines (Aapro et al., 2019; Hesketh et al., 2020; NCCN, 2022b; Roila et al., 2016). Guidelines from ASCO and MASCC/ESMO are consistent; NCCN guidelines share similarities, with a few notable variations.

(2) For patients receiving IV highly emetogenic chemotherapy agents

(a) NCCN recommends using a four-drug combination of olanzapine, an NK<sub>1</sub> receptor antagonist, a 5-HT<sub>3</sub> receptor antagonist, and dexamethasone prior to chemotherapy administration on day 1 (NCCN, 2022b).

i. Two additional treatment regimens are proposed as alternatives to the preferred four-drug combination regimen and include the following:

- A three-drug regimen consisting of olanzapine, palonosetron, and dexamethasone
  - A three-drug regimen consisting of an NK<sub>1</sub> receptor antagonist, 5-HT<sub>3</sub> receptor antagonist, and dexamethasone
- ii. Lorazepam may be combined with the aforementioned antiemetics to improve control in high-risk regimens (NCCN, 2022b).
  - iii. An H<sub>2</sub> antagonist or proton pump inhibitor can be added to minimize dyspepsia that can contribute to nausea (NCCN, 2022b).
  - iv. Antiemesis prophylaxis with combination olanzapine, aprepitant, and dexamethasone; olanzapine alone; or aprepitant and dexamethasone should be given on days 2–4. This varies depending on the prophylaxis treatment option given on day 1 (NCCN, 2022b).
- (b) ASCO also recommends using a four-drug combination consisting of a 5-HT<sub>3</sub> receptor antagonist, an NK<sub>1</sub> receptor antagonist, dexamethasone, and olanzapine prior to chemotherapy (Hesketh et al., 2020).
- i. Dexamethasone and olanzapine should be administered on days 2–4. Patients receiving an anthracycline and cyclophosphamide should only receive olanzapine on days 2–4.
  - ii. If aprepitant was administered on day 1, it should also be administered on days 2–3 (Hesketh et al., 2020).
- (c) MASCC/ESMO recommends a three-drug combination consisting of a 5-HT<sub>3</sub> receptor antagonist, an NK<sub>1</sub> receptor antagonist, and dexamethasone; the addition of olanzapine may be considered if nausea is of particular concern (Aapro et al., 2019; Roila et al., 2016).
- (d) Anthracycline plus cyclophosphamide regimens are classified as highly emetogenic chemotherapy (Aapro et al., 2019; Hesketh et al., 2020; NCCN, 2022b; Roila et al., 2016).
- (3) For patients receiving IV moderately emetogenic chemotherapy agents
- (a) NCCN recommends using a two-drug combination of a 5-HT<sub>3</sub> receptor antagonist and dexamethasone prior to chemotherapy on day 1 (NCCN, 2022b).
    - i. Two additional three-drug regimens are proposed as alternatives to the two-drug combination for certain patient-related risk factors or previous ineffective control of CINV with the 5-HT<sub>3</sub> and dexamethasone regimen.
      - Olanzapine, palonosetron, and dexamethasone (NCCN, 2022b)
      - An NK<sub>1</sub> receptor antagonist, a 5-HT<sub>3</sub> receptor antagonist, and dexamethasone (NCCN, 2022b)
    - ii. Lorazepam may be combined with the aforementioned antiemetics to improve control (NCCN, 2022b).
    - iii. The addition of an H<sub>2</sub> antagonist or proton pump inhibitor may be considered (NCCN, 2022b).
    - iv. Antiemesis prophylaxis consisting of dexamethasone, a 5-HT<sub>3</sub> receptor antagonist, olanzapine, or aprepitant with or without dexamethasone may be given on days 2 and 3. This will depend on the prophylaxis given on day 1 (NCCN, 2022b).
  - (b) ASCO and MASCC/ESMO recommend using a two-drug combination of a 5-HT<sub>3</sub> receptor antagonist and dexamethasone prior to chemotherapy on day 1 (Hesketh et al., 2020; Roila et al., 2016).
    - i. ASCO recommends an NK<sub>1</sub> receptor antagonist should be added to the two-drug regimen for patients receiving carboplatin dosed at an area under the curve greater than or equal to 4 mg/ml/min (Hesketh et al.,



- 2020). MASCC/ESMO guidelines agree with this approach but do not specify a dosing cutoff for carboplatin (Aapro et al., 2019; Roila et al., 2016).
- ii. Dexamethasone should be administered on days 2 and 3 if the patient is receiving chemotherapy associated with delayed nausea and vomiting, such as cyclophosphamide, doxorubicin, and oxaliplatin (Hesketh et al., 2020; Roila et al., 2016).
- (4) For patients receiving IV agents categorized as low emetogenic risk
    - (a) NCCN recommends a single dose of dexamethasone, metoclopramide, prochlorperazine, or a 5-HT<sub>3</sub> receptor antagonist prior to chemotherapy on day 1 (NCCN, 2022b).
      - i. Lorazepam may be combined with the aforementioned antiemetics to improve control (NCCN, 2022b).
      - ii. The addition of an H<sub>2</sub> antagonist or proton pump inhibitor may be considered (NCCN, 2022b).
    - (b) ASCO recommends a single dose of dexamethasone or a 5-HT<sub>3</sub> receptor antagonist prior to chemotherapy on day 1 (Hesketh et al., 2020).
  - (5) For patients receiving IV agents categorized as minimal emetogenic risk, no routine prophylaxis is recommended (Hesketh et al., 2020; NCCN, 2022b; Roila et al., 2016).
- d) Prevention and management of acute and delayed CINV related to oral antineoplastic administration (NCCN, 2022b)
- (1) For patients receiving oral agents categorized as high to moderate emetogenic risk
    - (a) Administer a 5-HT<sub>3</sub> receptor antagonist prior to taking oral chemotherapy and continue daily (NCCN, 2022b).
    - (b) Lorazepam may be combined with the aforementioned antiemetics to improve control (NCCN, 2022b).
    - (c) The addition of an H<sub>2</sub> antagonist or proton pump inhibitor may be considered (NCCN, 2022b).
  - (2) For patients receiving oral agents categorized as low to minimal emetogenic risk
    - (a) No routine prophylaxis is recommended, but antiemetics may be prescribed as needed. If the patient experiences nausea and vomiting, consider metoclopramide, prochlorperazine, or a 5-HT<sub>3</sub> receptor antagonist (NCCN, 2022b).
    - (b) Lorazepam may be combined with the aforementioned antiemetics to improve control (NCCN, 2022b).
    - (c) The addition of an H<sub>2</sub> antagonist or proton pump inhibitor may be considered (NCCN, 2022b).
- e) Treatment of delayed CINV
- (1) Delayed nausea is often more common and severe than acute nausea and is more difficult to treat (NCCN, 2022b).
  - (2) 5-HT<sub>3</sub> receptor antagonists, although effective for preventing acute vomiting, are not as effective for delayed vomiting.
  - (3) For patients receiving highly emetogenic chemotherapy or moderately emetogenic chemotherapy agents
    - (a) NCCN recommends dexamethasone be administered daily during chemotherapy and for two to three days after chemotherapy administration to help prevent delayed CINV (NCCN, 2022b).
    - (b) ASCO recommends dexamethasone and olanzapine on days 2–4 for patients receiving highly emetogenic chemotherapy agents unless they receive anthracycline and cyclophosphamide. In this case, ASCO recommends olanzapine only for days 2–4 (Hesketh et al., 2020).
    - (c) MASCC/ESMO recommends olanzapine specifically for concerns related to delayed nausea (Aapro et al., 2019).
  - (4) To prevent delayed CINV in patients receiving carboplatin, an NK<sub>1</sub> receptor antagonist should be given in combination with a 5-HT<sub>3</sub> receptor antagonist and dexamethasone (Aapro et al., 2019; Roila et al., 2016).
- f) Management of breakthrough CINV
- (1) Consider adding other antiemetic agents from different drug classifications, using caution to avoid overlapping side effects (Hesketh et al., 2020). Alternative agents not previously mentioned that can be used in breakthrough CINV management include dronabinol, nabilone, haloperi-



- dol, metoclopramide, scopolamine, prochlorperazine, and promethazine (NCCN, 2022b; see Table 15-2).
- (2) 5-HT<sub>3</sub> receptor antagonists are of limited effectiveness in managing breakthrough CINV when used following administration of long-acting or extended-release formulations of the same drug class, such as palonosetron, granisetron transdermal patch, or extended-release granisetron injection (NCCN, 2022b).
  - (3) Around-the-clock antiemetic dosing should be strongly considered for patients with breakthrough CINV (NCCN, 2022b).
  - (4) Persistent or intractable vomiting may preclude oral intake of medication; consider alternate administration routes (e.g., IV, rectal, transdermal) or formulations (e.g., orally dissolving films or tablets) of antiemetic agents. Oral granisetron is superior to transdermal granisetron for complete control of CINV and should be considered when feasible (Chua et al., 2020).
  - (5) Consider an H<sub>2</sub> antagonist or proton pump inhibitor for patients with dyspepsia (NCCN, 2022b).
  - (6) Monitor patient hydration status and electrolytes and correct as needed (NCCN, 2022b).
  - (7) Olanzapine may be an effective option for breakthrough CINV (Aapro et al., 2019; Chiu et al., 2016; Roila et al., 2016) and should be included in the prophylactic antiemesis regimen for patients with breakthrough nausea and vomiting (Hesketh et al., 2020).
  - (8) Due to limited evidence establishing superior efficacy as compared to newer antiemetic agents, as well as medical and legal concerns, medical cannabis and cannabidiol (CBD) oil are not recommended by NCCN, ASCO, or MASCC/ESMO in their most recent respective guidelines for prophylaxis or management of CINV. The quality of evidence supporting the use of U.S. Food and Drug Administration–approved cannabinoids for the treatment of CINV remains low (Garcia & Shamliyan, 2018; Hesketh, 2022b).
  - (9) Consider using nonpharmacologic interventions in conjunction with antiemetics.
8. Collaborative management: nonpharmacologic interventions
    - a) Behavioral interventions, including hypnosis, progressive muscle relaxation, biofeedback, yoga, systematic desensitization, music therapy, and acupuncture or acupressure, may be used as adjunct therapies to manage anticipatory CINV (NCCN, 2022b; Roila et al., 2016).
    - b) Management of patient expectations may help prevent chemotherapy-induced nausea (Lee et al., 2019).
    - c) Several nonpharmacologic interventions have been studied to prevent and manage CINV; however, effectiveness has not been established. These interventions may be considered for use in conjunction with antiemetics and include acupuncture, acupressure, aromatherapy, exercise, ginger, massage, therapeutic touch, and yoga (Lee et al., 2019; Marx et al., 2017).
  9. Dietary interventions (American Cancer Society, 2020; NCCN, 2022b)
    - a) Encourage patients to eat small, frequent meals and avoid skipping meals, as an empty stomach can worsen nausea.
    - b) Encourage patients to eat bland food or cold or room temperature food to minimize smells or tastes that may be unappealing.
    - c) Encourage patients to drink clear liquids (e.g., fruit juice, broth) and sip small amounts slowly throughout the day.
    - d) Encourage patients to avoid fried, spicy, fatty, or very sweet food and avoid food with strong odors.
    - e) Ensure that patients are eating enough protein and calories. A calorie-dense liquid replacement meal (e.g., protein shake) may be used.
    - f) Encourage patients to avoid overeating to minimize indigestion.
    - g) Encourage patients to use plastic forks and spoons if metal silverware causes a bitter taste.
    - h) Consider referral to an outpatient dietitian who specializes in cancer nutrition.
  10. Patient and family education
    - a) Instruct patients to take antiemetics as prescribed and notify the provider if they cannot do so for any reason.
    - b) Remind patients to take antiemetics before arriving for treatment. Ensure that antiemetics have been taken prior to administration of chemotherapy.
    - c) Encourage patients to notify the provider's office before antiemetic prescriptions have run out to ensure a refill can be dispensed without disrupting the medication supply.
    - d) Instruct patients to notify providers if nausea and vomiting persist for longer than 24 hours or if they cannot maintain fluid intake.

**TABLE 15-2.** Commonly Used Agents for Prevention and Treatment of Chemotherapy-Induced Nausea and Vomiting

| Classification         | Mechanism of Action                                                                                                                                           | Drug       | Route, Dose, and Schedule for Adult Patients                                                                                                                                                                    | Indications                                                                                                                                                                                                                                 | Side Effects                                                                                                                                                             | Nursing Considerations                                                                                                                                                                                                                          |
|------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Atypical antipsychotic | Acts on multiple receptor sites, including dopamine, histamine, serotonin, and acetylcholine-muscarine                                                        | Olanzapine | 2.5–10 mg PO daily<br>Consider a lower dose if previous dose caused excessive sedation.<br>Bedtime administration is recommended due to sedation effect, unless being used as premedication prior to treatment. | Prevention of acute and delayed nausea and vomiting                                                                                                                                                                                         | Dizziness, sedation, weight gain, altered cardiac conduction (prolonged QTc), anticholinergic effects (e.g., constipation, dry mouth, blurred vision, urinary retention) | The drug is contraindicated in patients with dementia. The risk of extrapyramidal symptoms is increased in patients receiving metoclopramide or haloperidol. (Alkermes, 2021; Camp-Sorrell, 2018; National Comprehensive Cancer Network, 2022b) |
| Benzodiazepine         | Acts as a central nervous system depressant; interferes with afferent nerves from the cerebral cortex by gamma-aminobutyric acid inhibition, causing sedation | Alprazolam | 0.5–1 mg PO given the night before treatment and repeated 1–2 hours before chemotherapy administration                                                                                                          | Prevention of anticipatory nausea and vomiting<br>Treatment for breakthrough chemotherapy-induced nausea and vomiting with anxiety component                                                                                                | Sedation, confusion, hyperactivity, agitation, dizziness, light-headedness, hallucinations                                                                               | Use a starting dose of 0.5 mg PO in older adult patients, patients with advanced liver disease, or other pertinent comorbidities. (Camp-Sorrell, 2018; National Comprehensive Cancer Network, 2022b; Pfizer, 2011)                              |
|                        |                                                                                                                                                               | Lorazepam  | 0.5–2 mg PO, sublingual, or IV every 6 hours<br>For anticipatory nausea and vomiting: 0.5–2 mg PO beginning the night before treatment and repeated 1–2 hours before chemotherapy administration                | In combination with other antiemetics as needed for acute or delayed nausea and vomiting<br>Prevention of anticipatory nausea and vomiting<br>Treatment for breakthrough chemotherapy-induced nausea and vomiting with an anxiety component | Sedation, confusion, hyperactivity, agitation, dizziness, light-headedness, hallucinations                                                                               | Use with caution in older adult patients and those with hepatic or renal dysfunction. (Camp-Sorrell, 2018; National Comprehensive Cancer Network, 2022b; West-Ward A Hikma Company, 2017)                                                       |
| Cannabinoid            | Activates cannabinoid receptors                                                                                                                               | Dronabinol | 5–10 mg capsules PO every 4–6 hours or 2.1–4.2 mg/m <sup>2</sup> oral solution, PO three to four times daily                                                                                                    | Treatment of breakthrough or refractory nausea and vomiting                                                                                                                                                                                 | Sedation, vertigo, euphoria, dysphoria, dry mouth, tachycardia, orthostasis, appetite stimulation                                                                        | The incidence of paranoid reactions or abnormal thinking increases with maximum doses. (Camp-Sorrell, 2018; National Comprehensive Cancer Network, 2022b)                                                                                       |

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**TABLE 15-2.** Commonly Used Agents for Prevention and Treatment of Chemotherapy-Induced Nausea and Vomiting (*Continued*)

| Classification                  | Mechanism of Action                                                            | Drug          | Route, Dose, and Schedule for Adult Patients                                                                                                                                                                                                                                      | Indications                                                 | Side Effects                                                                               | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|---------------------------------|--------------------------------------------------------------------------------|---------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------|--------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cannabinoid<br>( <i>Cont.</i> ) |                                                                                | Nabilone      | 1–2 mg PO twice daily<br>The maximum recommended dose is 6 mg given in divided doses three times daily.                                                                                                                                                                           | Treatment of breakthrough or refractory nausea and vomiting | Sedation, vertigo, euphoria, dysphoria, dry mouth, tachycardia, orthostasis                | The incidence of paranoid reactions or abnormal thinking increases with maximum doses. (Camp-Sorrell, 2018; National Comprehensive Cancer Network, 2022b; Unimed Pharmaceuticals, 2004)                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Corticosteroid                  | Antiprostaglandin synthesis activity; mechanism of antiemetic activity unknown | Dexamethasone | For moderate to high emetogenic risk: 12 mg IV or PO day 1 of chemotherapy, then 8 mg IV or PO days 2–4<br>For low emetogenic risk: 8–12 mg PO or IV once<br>For extended delayed chemotherapy-induced nausea and vomiting: Consider 12 mg PO/IV daily as clinically appropriate. | Prevention of acute and delayed nausea and vomiting         | Insomnia, anxiety, acne, euphoria, flushing, hyperglycemia, dyspepsia                      | Administer in the morning to minimize insomnia.<br>Use with caution in patients with diabetes mellitus.<br>Dexamethasone metabolism may be affected by the administration of fosaprepitant, aprepitant, and netupitant, and the dosage of dexamethasone may require adjustment.<br>Administer slowly over at least 10 minutes to prevent perianal or vaginal burning or itching.<br>Avoid corticosteroid antiemetic premedication for 3–5 days prior and to 90 days following chimeric antigen receptor T-cell therapy. (Camp-Sorrell, 2018; Fresenius Kabi, 2014; National Comprehensive Cancer Network, 2022b) |
| Dopamine antagonist             | Blocks dopamine receptors                                                      | Haloperidol   | 0.5–2 mg PO or IV every 4–6 hours                                                                                                                                                                                                                                                 | Treatment of breakthrough nausea and vomiting               | Sedation, extrapyramidal symptoms, dystonia, dizziness, orthostasis, prolonged QT interval | Extrapyramidal symptoms are more common in younger patients.<br>The drug is highly sedating. (Camp-Sorrell, 2018; National Comprehensive Cancer Network, 2022b; Ortho-Biotech Products, 2005)                                                                                                                                                                                                                                                                                                                                                                                                                    |

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**TABLE 15-2.** Commonly Used Agents for Prevention and Treatment of Chemotherapy-Induced Nausea and Vomiting (*Continued*)

| Classification                          | Mechanism of Action | Drug             | Route, Dose, and Schedule for Adult Patients                                                                     | Indications                                                                                          | Side Effects                                                                  | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                            |
|-----------------------------------------|---------------------|------------------|------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Dopamine antagonist<br>( <i>Cont.</i> ) |                     | Metoclopramide   | 10–40 mg PO or IV every 4–6 hours                                                                                | Prevention of acute or delayed nausea and vomiting<br>Treatment of breakthrough nausea and vomiting  | Sedation, extrapyramidal symptoms, dystonia, dizziness, orthostasis, diarrhea | The drug increases gut motility and may be given to manage gastroparesis.<br>The risk of tardive dyskinesia increases with the duration of treatment and increasing cumulative dose.<br>The U.S. Food and Drug Administration recommends short-term use (< 12 weeks) to minimize risk.<br>(Alaven Pharmaceutical, 2009; Baxter Oncology, 2010b; Camp-Sorrell, 2018; National Comprehensive Cancer Network, 2022b) |
|                                         |                     | Prochlorperazine | Varied dosage; 5–10 mg PO or IV every 6 hours<br>Also available as 25 mg suppositories per rectum every 12 hours | Prevention of acute and delayed nausea and vomiting<br>Treatment of breakthrough nausea and vomiting | Sedation, extrapyramidal symptoms, dystonia, dizziness, orthostasis           | The drug is sedating.<br>(Baxter Oncology, 2010a; Camp-Sorrell, 2018; Glaxo SmithKline, 2004; National Comprehensive Cancer Network, 2022b)                                                                                                                                                                                                                                                                       |
|                                         |                     | Promethazine     | 12.5–25 mg PO every 6 hours<br>Also available as 25 mg suppositories per rectum every 6 hours                    | Prevention of acute and delayed nausea and vomiting<br>Treatment of breakthrough nausea and vomiting | Sedation, extrapyramidal symptoms, dystonia, dizziness, orthostasis           | The drug is highly sedating. IV administration is generally avoided due to the risk of severe tissue injury with extravasation (necrosis).<br>(Camp-Sorrell, 2018; National Comprehensive Cancer Network, 2022b; Wyeth Pharmaceuticals, 2004)                                                                                                                                                                     |

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**TABLE 15-2.** Commonly Used Agents for Prevention and Treatment of Chemotherapy-Induced Nausea and Vomiting (*Continued*)

| Classification          | Mechanism of Action                   | Drug          | Route, Dose, and Schedule for Adult Patients                                                                           | Indications                                         | Side Effects                                                                                                                 | Nursing Considerations                                                                                                                                                                                                                                                                                                                                         |
|-------------------------|---------------------------------------|---------------|------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Neurokinin-1 antagonist | Neurokinin-1 receptor antagonist      | Aprepitant    | 125 mg PO on day 1 of chemotherapy, then 80 mg PO on days 2 and 3<br>Also available as a 130 mg IV injectable emulsion | Prevention of acute and delayed nausea and vomiting | Fatigue, headache, dyspepsia, decreased appetite, hiccups                                                                    | When administered with dexamethasone, aprepitant causes an increase in dexamethasone serum levels. Consider decreasing dose of dexamethasone by 50%. Aprepitant injectable emulsion is not interchangeable with the IV formulation of fosaprepitant. (Camp-Sorrell, 2018; Heron Therapeutics, 2022; Merck, 2010; National Comprehensive Cancer Network, 2022b) |
|                         |                                       | Fosaprepitant | 150 mg IV once on day 1                                                                                                | Prevention of acute and delayed nausea and vomiting | Fatigue, infusion site reactions, infusion-related hypersensitivity reactions, diarrhea, hiccups, lack of appetite, headache | When administered with dexamethasone, fosaprepitant causes an increase in dexamethasone serum levels. Consider decreasing dose of dexamethasone by 50%. (Camp-Sorrell, 2018; Merck, 2018; National Comprehensive Cancer Network, 2022b)                                                                                                                        |
|                         |                                       | Rolapitant    | 180 mg PO once on day 1                                                                                                | Prevention of acute and delayed nausea and vomiting | Neutropenia, anemia, hiccups, abdominal pain, decreased appetite, dizziness, dyspepsia, urinary tract infection, stomatitis  | Dexamethasone dose does not need to be adjusted. It can be given with or without meals. (Camp-Sorrell, 2018; National Comprehensive Cancer Network, 2022b; Tesaro, 2017)                                                                                                                                                                                       |
| Serotonin inhibitors    | 5-HT <sub>3</sub> receptor antagonist | Dolasetron    | 100 mg PO once on days chemotherapy is administered                                                                    | Prevention of acute and delayed nausea and vomiting | Headache, diarrhea, dizziness, fatigue, prolonged QT interval, cardiac arrhythmia                                            | IV dolasetron is not recommended because it is associated with an increased risk of cardiac arrhythmias. (Camp-Sorrell, 2018; National Comprehensive Cancer Network, 2022b; Sanofi-Aventis U.S., 2013)                                                                                                                                                         |

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**TABLE 15-2.** Commonly Used Agents for Prevention and Treatment of Chemotherapy-Induced Nausea and Vomiting (*Continued*)

| Classification                           | Mechanism of Action | Drug                                   | Route, Dose, and Schedule for Adult Patients                                                                                                                                                                                                                                                                                                               | Indications                                         | Side Effects                                                                                           | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                   |
|------------------------------------------|---------------------|----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|--------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Serotonin inhibitors<br>( <i>Cont.</i> ) |                     | Granisetron                            | 2 mg PO, or 0.01 mg/kg (maximum 1 mg) IV once prior to chemotherapy<br>IV or PO dose may be repeated on subsequent days that chemotherapy is administered.                                                                                                                                                                                                 | Prevention of acute and delayed nausea and vomiting | Headache, nausea, constipation, vomiting, weakness, prolonged QT interval                              | IV drug formulation is not interchangeable for use as an extended-release formulation for SC injection administration.<br>The optimal effect of use is seen with scheduled dosing, not as needed dosing.<br>(Camp-Sorrell, 2018; National Comprehensive Cancer Network, 2022b; Roche Pharmaceuticals, 1999; Teva Pharmaceuticals, 2011)                                  |
|                                          |                     | Granisetron extended-release injection | 10 mg SC once to the back upper arm or in the abdomen at least 30 minutes prior to chemotherapy on day 1<br>Do not administer more frequently than once every 7 days.                                                                                                                                                                                      | Prevention of acute and delayed nausea and vomiting | Injection site reaction, constipation, fatigue, headache, diarrhea, abdominal pain, allergic reactions | Inject the product slowly; the product is viscous and may take 20–30 seconds to administer.<br>A topical anesthetic may be applied at the injection site prior to administration.<br>(Camp-Sorrell, 2018; Heron Therapeutics, 2016; National Comprehensive Cancer Network, 2022b)                                                                                        |
|                                          |                     | Granisetron transdermal                | Transdermal patch containing 34.3 mg of granisetron<br>One patch delivers 3.1 mg per 24 hours. Apply a single patch to the upper outer arm a minimum of 24–48 hours before chemotherapy.<br>The patch can be worn for up to 7 days (depending on the duration of the regimen).<br>Remove the patch a minimum of 24 hours after completion of chemotherapy. | Prevention of acute and delayed nausea and vomiting | Headache, nausea, constipation, vomiting, weakness                                                     | Remove the patch if severe skin reactions occur (e.g., allergic, erythematous, macular, or papular rash, pruritus).<br>Instruct patients to avoid direct exposure of the application site to natural and artificial light while wearing the patch and for 10 days after removal.<br>(Camp-Sorrell, 2018; National Comprehensive Cancer Network, 2022b; ProStrakan, 2015) |

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**TABLE 15-2.** Commonly Used Agents for Prevention and Treatment of Chemotherapy-Induced Nausea and Vomiting (*Continued*)

| Classification                           | Mechanism of Action                                                    | Drug                       | Route, Dose, and Schedule for Adult Patients                                                                                        | Indications                                         | Side Effects                                                                    | Nursing Considerations                                                                                                                                                                                                                                                                          |
|------------------------------------------|------------------------------------------------------------------------|----------------------------|-------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|---------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Serotonin inhibitors<br>( <i>Cont.</i> ) |                                                                        | Ondansetron                | 16–24 mg PO or 8–16 mg IV once on day of chemotherapy<br>Orally disintegrating tablet formulation: 8 mg<br>Oral soluble film: 24 mg | Prevention of acute and delayed nausea and vomiting | Headache, fatigue, malaise, constipation, drowsiness, sedation, QT prolongation | PO ondansetron has a lower risk of cardiac arrhythmia than IV ondansetron. A single dose larger than 16 mg of ondansetron is not recommended because of the increased risk of prolonged QT interval. (Camp-Sorrell, 2018; Glaxo SmithKline, 2016; National Comprehensive Cancer Network, 2022b) |
|                                          |                                                                        | Palonosetron               | 0.25 mg IV 30 minutes prior to chemotherapy on day 1                                                                                | Prevention of acute and delayed nausea and vomiting | Headache, constipation                                                          | The mean terminal elimination half-life is approximately 40 hours. IV palonosetron is more effective for preventing delayed nausea than other 5-HT <sub>3</sub> receptor antagonists. (Camp-Sorrell, 2018; MGI Pharma, 2006; National Comprehensive Cancer Network, 2022b)                      |
| Combination                              | Neurokinin-1 receptor antagonist/5-HT <sub>3</sub> receptor antagonist | Netupitant/palonosetron    | Netupitant 300 mg and palonosetron 0.5 mg (as a fixed combination product) PO given once on day 1                                   | Prevention of acute and delayed nausea and vomiting | Headache, fatigue, weakness                                                     | Monitor patients for hypersensitivity reactions. Avoid use in patients with severe hepatic impairment or end-stage renal disease. (Camp-Sorrell, 2018; Helsinn Therapeutics, 2021a, 2021b; National Comprehensive Cancer Network, 2022b)                                                        |
|                                          |                                                                        | Fosnetupitant/palonosetron | Fosnetupitant 235 mg and palonosetron 0.25 mg (as a fixed combination product) IV given once on day 1                               | Prevention of acute and delayed nausea and vomiting | Headache, fatigue, weakness                                                     | Monitor patients for hypersensitivity reactions. Avoid use in patients with severe hepatic impairment or end-stage renal disease. (Camp-Sorrell, 2018; Helsinn Therapeutics, 2021a, 2021b; National Comprehensive Cancer Network, 2022b)                                                        |

5-HT<sub>3</sub>—5-hydroxytryptamine-3; IV—intravenous; PO—by mouth; QTc—QT interval corrected; SC—subcutaneous



- e) Refer patients to educational materials, such as NCI's (2018) *Eating Hints: Before, During and After Cancer Treatment*.

## B. Anorexia and cachexia

### 1. Overview

- a) Anorexia is the loss of a desire to eat (NCI, 2022c).
- b) Cachexia derives from the Greek words *kakos* and *hexis*, meaning "bad condition" (Peixoto da Silva et al., 2020). Cancer cachexia is "a multifactorial syndrome characterised by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment" (Fearon et al., 2011, p. 490; see Figure 15-5).

### 2. Pathophysiology: Anorexia and cachexia result from a complicated process involving numerous physiologic and psychological factors.

#### a) Tumor effects

- (1) Ascites and obstructions of the bowel and GI tract can lead to nutrient malabsorption, nausea, vomiting, and pain (e.g., tumors causing dysphagia or affecting GI function) (Archid et al., 2019).
- (2) Substances released by the tumor can lead to inflammation and satiety, contributing to anorexia and cachexia (Mattox, 2017; Peixoto da Silva et al., 2020).
  - (a) Proinflammatory cytokines such as interleukin-1 (IL-1), IL-6, IL-8, tumor necrosis factor-alpha, and interferon gamma (Peixoto da Silva et al., 2020)
  - (b) Lactate (Peixoto da Silva et al., 2020)
  - (c) Parathyroid hormone-related peptide (Peixoto da Silva et al., 2020)

- (3) Hypercalcemia secondary to bony involvement or paraneoplastic syndrome may lead to nausea, vomiting, and anorexia (Feldenzer & Sarno, 2018).

- (4) Decreased hypothalamic response signals from functional damage can reduce appetite (Peixoto da Silva et al., 2020).

- (5) Low protein and albumin levels lead to more extracellular water, and less intracellular water causes low oncotic pressure and increases weight loss (Schwarz et al., 2017).

#### b) Treatment effects

- (1) Surgery may result in gastroparesis, dumping syndrome, malabsorption, obstruction, and fluid and electrolyte abnormalities (Granda-Cameron & Lynch, 2018).
- (2) Chemotherapy and radiation therapy side effects can occur, including nausea, vomiting, mucositis, taste changes, xerostomia, constipation, and diarrhea (Peixoto da Silva et al., 2020).
- (3) Combination therapy may result in a higher number of adverse effects.

#### c) Psychosocial effects

- (1) Cancer-related depression often coexists with anorexia and cachexia, especially in patients with late-stage disease or multiple symptoms. The prevalence of depression among patients with cancer is estimated to be 15%–25% (Weber & O'Brien, 2017).
- (2) Anxiety, fear, grief, fatigue, pain, and reaction to body image changes may contribute to anorexia (Weber & O'Brien, 2017).
- (3) Cachexia results in decreased survival and poor response to treatment (NCI, 2022c).

### 3. Types of anorexia and cachexia

- a) Anorexia (Laviano, Koverech, & Seelaender, 2017)

**FIGURE 15-5. Cancer Cachexia**

#### Diagnostic Criteria

- Weight loss > 5% over the past 6 months; or
- Body mass index < 20 kg/m<sup>2</sup> and any degree of weight loss > 2%; or
- Appendicular skeletal muscle index consistent with sarcopenia (another wasting syndrome) and weight loss of > 2%

#### Stages of Cancer Cachexia

- Precachexia: weight loss of ≤ 5%, along with other symptoms such as impaired glucose tolerance or anorexia
- Cachexia: weight loss > 5% or other symptoms and conditions consistent with the diagnostic criteria for cachexia
- Refractory cachexia: patients experiencing cachexia who are no longer responsive to cancer treatment, have a low performance score, and have a life expectancy of < 3 months

Note. Based on information from Fearon et al., 2011.

- (1) Primary anorexia results from an altered body image perception, resulting in a refusal to eat.
  - (2) Secondary anorexia results from acute and chronic diseases creating an inflammatory response.
- b) Cachexia (Granda-Cameron & Lynch, 2018)
  - (1) Primary cachexia results from the tumor causing an inflammatory response and multiple metabolic alterations originating from tumor cells and activated immune cells.
  - (2) Secondary cachexia results from treatment affecting a patient with cancer's nutritional intake.
4. Incidence
  - a) Anorexia
    - (1) Anorexia is present in 15%–25% of patients with cancer at diagnosis and 26% of those receiving chemotherapy (NCI, 2022c).
    - (2) It is the fourth most common symptom in advanced cancer and only surpassed by pain, fatigue, and weakness (Peixoto da Silva et al., 2020).
  - b) Cachexia
    - (1) Prevalence in patients with cancer is widely variable (12%–85%) (Granda-Cameron & Lynch, 2018).
    - (2) Incidence varies based on the cancer type (Ni & Zhang, 2020; Peixoto da Silva et al., 2020).
      - (a) Gastric or pancreatic cancer: more than 80%
      - (b) Colon, lung, and prostate cancers and non-Hodgkin lymphoma: 50%–61%
      - (c) Breast cancer, advanced head and neck cancers, some leukemias, Hodgkin lymphoma, and sarcoma: 40%
    - (3) Approximately 20%–30% of cancer-related deaths are attributed to cachexia, a sign of poor prognosis (Ni & Zhang, 2020; Son et al., 2020).
5. Risk factors
  - a) Solid tumors, especially gastric and pancreatic cancers (Ni & Zhang, 2020; Peixoto da Silva et al., 2020)
  - b) Comorbidities with other chronic or end-stage diseases associated with cachexia, such as AIDS, congestive heart failure, chronic obstructive pulmonary disease, rheumatoid arthritis, and tuberculosis (Peixoto da Silva et al., 2020)
  - c) Very young and older adults
  - d) Depression
  - e) Cancer treatments
    - (1) Chemotherapy, immunotherapy, and targeted therapy
      - (a) Platinum-based treatments contribute to weight loss and muscle wasting (Moreira-Pais et al., 2018).
      - (b) Tyrosine kinase inhibitors (TKIs), such as sorafenib or lenvatinib, may contribute to loss of skeletal muscle (Uchikawa et al., 2020).
    - (2) Surgical procedures, such as esophagectomy and gastrectomy, can cause early satiety (NCI, 2022c).
    - (3) Radiation (Arends et al., 2017)
      - (a) Head and neck or esophagus radiation can cause mucositis and decreased food intake.
      - (b) Pelvic area radiation can cause GI symptoms.
  - f) Cancer and its treatment side effects, such as emesis, dysphagia, mucositis, reduced or altered taste, and pain (Peixoto da Silva et al., 2020)
6. Clinical manifestations
  - a) Anorexia is an involuntary weight loss of greater than 5% of usual weight (Biswas & Acharyya, 2020).
  - b) It is clinically diagnosed when patients report a negative appetite change (Laviano, Koverech, & Seelaender, 2017).
    - (1) Changes in taste and smell
    - (2) Early satiety
  - c) Changes in GI tract function (Peixoto da Silva et al., 2020)
    - (1) Dysmotility
    - (2) Inactivation of bile salts or pancreatic enzymes
    - (3) Partial or complete obstruction
  - d) Loss of muscle mass and adipose tissue
  - e) Fatigue and weakness
  - f) Immune system impairment
  - g) Metabolic dysfunction
  - h) Hypoalbuminemia
7. Assessment: Subjective reporting of anorexia in patients with cancer makes assessment difficult; no consensus exists on specific methods for assessment (Abraham et al., 2019).
  - a) Dietary intake and nutrition
    - (1) Perform a nutritional assessment, including a dietary intake evaluation.
    - (2) Patients may keep a food and fluid diary or recall nutritional intake (Arends et al., 2017).
    - (3) Use a validated nutrition screening tool (Arends et al., 2017; Dijksterhuis et al., 2021).

- (a) Nutrition Risk Screening 2002 (NRS-2002) detects the early benefit of nutritional intervention and is performed within 48 hours of hospitalization (Rabito et al., 2017).
  - (b) Malnutrition Universal Screening Tool (MUST) identifies malnutrition in community settings and hospitals by reviewing nutritional status and disease-related factors (Rabito et al., 2017).
  - (c) Malnutrition Screening Tool (MST) is a quick and straightforward three-question tool that can be completed upon admission by staff, caregivers, or patients (Rabito et al., 2017).
  - b) Measuring body composition (Arends et al., 2017; Ni & Zhang, 2020)
    - (1) Computed tomography (CT) measurement at the level of the third lumbar vertebrae has a high level of accuracy and specificity and is the gold standard.
    - (2) Magnetic resonance imaging is the equivalent of a CT scan without radiation exposure, but it can be costly.
    - (3) Dual x-ray absorptiometry scans appendicular muscles with low radiation exposure and cost, but it can overestimate lean body mass.
    - (4) Anthropometric methods are not as accurate, and it is difficult to differentiate between lean body mass and fat tissue (Casadei & Kiel, 2021).
      - (a) Weight: Consider correcting weight when excess fluid may be present (i.e., pleural effusions, ascites, edema).
      - (b) Height with a stadiometer
      - (c) Body circumference of waist, hip, and limbs
      - (d) Body mass index
      - (e) Skinfold thickness
        - i. Triceps skinfold thickness estimates body fat.
        - ii. Mid-arm muscle circumference estimates muscle mass.
    - (5) Bioelectrical impedance analysis
  - c) Assess physical performance with the Eastern Cooperative Oncology Group Performance Status Scale or Karnofsky Performance Status Scale (Arends et al., 2017).
  - d) Assess functional status (Meregaglia et al., 2019).
    - (1) Functional Assessment of Anorexia-Cachexia Therapy is a 39-item, question-validated tool to assess patient status.
      - (2) Functional status tools include symptom distress and quality-of-life questions.
    - e) Grading: See Table 15-3 for NCI's anorexia grading scale.
    - f) Assess laboratory results (Ni & Zhang, 2020).
      - (1) Evaluate inflammatory markers and cytokines.
        - (a) Examples include hemoglobin, albumin, C-reactive protein, ghrelin, adiponectin, leptin, insulin-like growth factor 1, IL-1, IL-6, and tumor necrosis factor- $\alpha$ .
        - (b) The best indicators of cancer cachexia are albumin and C-reactive protein levels.
      - (2) Evaluate for endocrine abnormalities, such as thyroid dysfunction, metabolic abnormalities, and hypogonadism (NCCN, 2022c).
    - g) Assess for social or financial factors that may inhibit adequate nutritional intake (NCCN, 2022c).
    - h) Reconcile medications to assess for any that may interfere with intake (NCCN, 2022c).
8. Collaborative management and effect on clinical outcomes: Treatment of anorexia should focus on treating any reversible causes (NCCN, 2022c). Although no standard of care treatment exists for cancer cachexia, treatment is the primary objective (Son et al., 2020). Identifying and treating cancer cachexia aims to improve treatment tolerability, improve survival, and optimize quality of life (Roeland et al., 2020).
- a) Symptom management: Management of symptoms, such as nausea and vomiting, mucositis, oral candidiasis, diarrhea, constipation, taste changes, dysphagia, xerostomia, fatigue, pain, and depression, may improve anorexia.
  - b) Pharmacologic interventions (NCCN, 2022c)
    - (1) Reduced or lack of appetite
      - (a) Megestrol acetate: 200–600 mg PO daily, increasing to 400–800 mg daily at the end of life
      - (b) Olanzapine: 5 mg PO daily
      - (c) Dexamethasone: 3–4 mg PO daily
      - (d) Cannabinoids may be considered.
    - (2) Early satiety: metoclopramide 5–10 mg PO four times daily 30 minutes before meals and at bedtime
    - (3) Depression: mirtazapine 7.5–30 mg oral PO every night at bedtime
  - c) Nonpharmacologic interventions (Dev et al., 2017; NCCN, 2022c)
    - (1) Nutritional counseling and nutrition (Arends et al., 2017; Roeland et al., 2020)

**TABLE 15-3.** Common Terminology Criteria for Adverse Events Grading for Anorexia

| Adverse Event | Grade                                                |                                                                                                             |                                                                                                                                            |                                                              |       |
|---------------|------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|-------|
|               | 1                                                    | 2                                                                                                           | 3                                                                                                                                          | 4                                                            | 5     |
| Anorexia      | Loss of appetite without alteration in eating habits | Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated | Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); tube feeding or TPN indicated | Life-threatening consequences; urgent intervention indicated | Death |

TPN—total parenteral nutrition

Note. From *Common Terminology Criteria for Adverse Events* [v.5.0], by National Cancer Institute Cancer Therapy Evaluation Program, 2017 ([https://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/docs/CTCAE\\_v5\\_Quick\\_Reference\\_5x7.pdf](https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf)). In the public domain.

- (a) Refer to a registered dietitian for early and regular assessment and counseling.
  - (b) Provide high-calorie and high-protein oral supplements as needed and tolerated.
  - (c) Enteral or parenteral nutrition should not be routinely offered to treat cachexia in patients with advanced cancer. A short-term trial may be considered in a select group of patients with malabsorptive disorders, reversible bowel obstruction, or undergoing curative treatment.
    - i. Enteral: A nasogastric tube or percutaneous endoscopic gastrostomy can be used for patients with a functioning bowel. Complications include aspiration pneumonia, electrolyte abnormalities, diarrhea, and infection.
    - ii. Parenteral: Total parenteral nutrition (requiring central venous access) and peripheral parenteral nutrition can be used. Complications include an increased infection rate.
  - (d) Consider swallowing evaluation (NCCN, 2022c).
- (2) Physical activity
- (a) Physical activity can preserve muscle mass and function, reduce systemic inflammation, and decrease systemic catabolism (Ni & Zhang, 2020).
  - (b) Exercise programs should include resistance and aerobic exercises that are realistic and achievable (Laviano, Di Lazzaro Giraldo, & Koverech, 2017).
- (3) Psychosocial support
- (a) Monitor for depression, fatigue, living alone, low income, and access to food, which may affect nutritional intake, and refer to appropriate resources (Williams, 2020).
  - (b) Physical changes associated with weight loss can cause patient and family distress (Buonaccorso et al., 2021). Refer to psychosocial and emotional support as needed.
  - (c) Early consultation of a palliative care team has shown to improve outcomes (Dev et al., 2017; Schwarz et al., 2017).
  - (4) Integrative medicine: Complementary and alternative medicine may be helpful, including acupuncture, aromatherapy, mind-body therapies, music therapy, prayer, and spiritual uplifting (NCI, 2021a; Zhang et al., 2018).
9. Patient and family education
- a) Provide education on the overall condition and the risk and benefits of all treatment options (NCCN, 2022c).
  - b) Instruct patients to take medications as prescribed for symptom management and notify providers of symptoms that may be affecting dietary intake.
  - c) Provide examples of high-protein, high-calorie, and nutrient-dense foods (Roeland et al., 2020) and refer to additional educational print resources, such as NCI's (2018) *Eating Hints: Before, During and After Cancer Treatment*.
  - d) Encourage small, frequent meals and snacks in an attractive setting.
  - e) Monitor and record weight weekly, using the same scale at the same time of the day, and notify providers of any weight decreases.

- f) Advise patients that a lack of interest in food is normal at the end of life and that nutritional support is insufficient to reverse weight loss as cancer progresses (NCCN, 2022c). Encourage involvement in family meals, even if patients have no appetite, and offer support to patients, families, and caregivers to cope with decreased intake (Buonaccorso et al., 2021).
- g) Encourage patients to engage in physical activity, including aerobic and resistance exercise (Buonaccorso et al., 2021).

## C. Diarrhea

### 1. Overview

- a) Definition: Diarrhea is defined as loose or watery stools three or more times daily that may be acute, chronic, or persistent (National Institute of Diabetes and Digestive and Kidney Diseases, 2016). Diagnostic criteria include greater than 75% water content, increase in daily stool weight, and frequency (Pessi et al., 2014).
  - (1) Classification based on duration (National Institute of Diabetes and Digestive and Kidney Diseases, 2016)
    - (a) Acute: Diarrhea lasts one to two days and typically resolves independently.
    - (b) Persistent: Diarrhea lasts two to four weeks.
    - (c) Chronic: Diarrhea lasts at least four weeks and has potentially transient symptoms.
  - (2) Classification based on grade (NCI Cancer Therapy Evaluation Program [CTEP], 2017; see Table 15-4)
- b) Antineoplastic treatment-induced diarrhea
  - (1) Diarrhea in patients with cancer is associated with the disease and its treatments, including radiation therapy, chemotherapy, targeted therapy, and immunotherapy,

as well as graft-versus-host disease (Bossi et al., 2018).

- (2) Classification of chemotherapy-induced diarrhea based on intensity (Bossi et al., 2018)
  - (a) Uncomplicated: grade 1–2 toxicity without additional signs or symptoms
  - (b) Complicated: grade 3–4 diarrhea or grade 1–2 diarrhea with one or more of the following: cramping, nausea, vomiting, fever, bleeding, dehydration, sepsis, neutropenia, or decreased performance status
- (3) Chemotherapy-induced diarrhea contributes to treatment alterations (60%), interference in daily activities (30%), dose delays (28%), treatment discontinuation (15%), and death related to dehydration (5%) (McQuade et al., 2016).

- 2. Pathophysiology: The pathophysiology and etiology of diarrhea in patients with cancer can be multifaceted. All possible causes of diarrhea need to be considered to treat patients appropriately.

### a) Classifications of diarrhea

#### (1) Osmotic diarrhea

- (a) Osmotic diarrhea usually is related to injury to the gut, dietary factors, or problems with digestion.
- (b) Water is drawn into the intestinal lumen, resulting in increased stool volume and weight.
- (c) Lactose intolerance is an example of this type of diarrhea.
- (d) New-onset lactose intolerance can occur in patients undergoing cancer treatment (Andreyev et al., 2014).
- (e) Osmotic diarrhea is associated with large stool volumes and sometimes is improved with fasting or elimina-

**TABLE 15-4.** Common Terminology Criteria for Adverse Events Grading for Diarrhea

| Adverse Event | Grade                                                                                             |                                                                                                                                                         |                                                                                                                                                                              |                                                              |       |
|---------------|---------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|-------|
|               | 1                                                                                                 | 2                                                                                                                                                       | 3                                                                                                                                                                            | 4                                                            | 5     |
| Diarrhea      | Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline | Increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental activities of daily living | Increase of ≥7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care activities of daily living | Life-threatening consequences; urgent intervention indicated | Death |

Note. From *Common Terminology Criteria for Adverse Events* [v5.0], by National Cancer Institute Cancer Therapy Evaluation Program, 2017 ([https://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/docs/CTCAE\\_v5\\_Quick\\_Reference\\_5x7.pdf](https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf)). In the public domain.

- tion of the causative factor (e.g., lactose, sorbitol) (Andreyev et al., 2012, 2014; Burgers et al., 2020).
- (2) Secretory diarrhea
    - (a) The small and large intestines secrete more fluids and electrolytes than can be absorbed.
    - (b) Infection and inflammation of the gut; damage to the gut caused by chemotherapy, radiation therapy, or graft-versus-host disease; and certain endocrine tumors can cause secretory diarrhea.
    - (c) The imbalance between absorption and secretion leads to the production of a large volume of fluid and electrolytes in the small bowel.
    - (d) This type of diarrhea is associated with large volumes and may require a bowel rest with parenteral nutrition followed by slow diet progression as tolerated (Muehlbauer, 2014).
  - (3) Exudative diarrhea
    - (a) This type is caused by alterations in mucosal integrity, epithelial loss, enzyme destruction, and defective absorption of the colon.
    - (b) Mucosal inflammation and ulceration caused by inflammatory diseases, cancers, and cancer treatment may result in the outpouring of plasma, proteins, mucus, and blood into the stool, which can result in exudative diarrhea (Bisanz et al., 2010).
  - (4) Inflammatory diarrhea
    - (a) Inflammatory diarrhea develops from invasive or toxin-producing bacteria causing impaired mucosal integrity that may result in tissue damage (Barr & Smith, 2014).
    - (b) It is characterized by fecal leukocytes, lactoferrin/calprotectin, or blood (Burgers et al., 2020).
  - (5) Dysentery is diarrhea characterized by blood in the stool (Schmidt-Hieber et al., 2017).
  - (6) Altered GI motility is seen in some endocrine disorders, such as hyperthyroidism and diabetes mellitus. Other causes can include small intestinal bacterial overgrowth and certain bile acids (Burgers et al., 2020; Yde et al., 2018).
- b) Pathophysiologic mechanisms by antineoplastic agent category
- (1) Chemotherapy (Andreyev et al., 2014)
    - (a) The metabolic by-products of agents can cause direct mucosal damage and toxicity (e.g., SN-38G from irinotecan), mitotic arrest of cells in the GI tract resulting in alterations to the osmotic gradient (e.g., with 5-fluorouracil), or stimulation of inflammatory cytokines, tumor necrosis factor-alpha, and prostaglandins.
    - (b) Diarrhea can also be cholinergically mediated, as with irinotecan (early onset).
    - (c) Osmotic diarrhea by way of development of lactose intolerance is seen in approximately 10% of patients treated with 5-fluorouracil and generally resolves after treatment.
  - (2) Targeted therapy (Bossi et al., 2018)
    - (a) Secretory diarrhea is associated with excessive chloride secretion related to many anti-epidermal growth factor receptor (EGFR) agents; this toxicity may also be amplified with combination radiation therapy.
    - (b) Ischemic mucosal damage may result from agents such as TKIs.
    - (c) Though the exact mechanism is unknown, drugs that target angiogenesis, such as vascular endothelial growth factor (VEGF)-targeted therapies, can lead to intestinal wall ulceration and disturbed platelet-endothelial cell homeostasis, causing inflammation leading to diarrhea.
    - (d) Mammalian target of rapamycin (mTOR) inhibitors are associated with gut microflora disequilibrium and malabsorption.
  - (3) Immunotherapy: Immune-mediated colitis, as well as resulting diarrhea, is a primary immune-related adverse event associated with immunotherapies, specifically checkpoint inhibitors, and may present as acute or delayed (often five to seven weeks after therapy) (Spain et al., 2016).
- c) Differential diagnosis for diarrhea in patients with cancer (Schmidt-Hieber et al., 2017)
- (1) Paraneoplastic diarrhea is rare and triggered by the secretion of vasoactive intestinal polypeptide, leading to watery diarrhea and electrolyte alterations.



- (2) Malabsorption
    - (a) Fat malabsorption: Steatorrhea or stools being described as oily, pale, foul-smelling, or difficult to flush may indicate fat maldigestion (Fernandes & Andreyev, 2020). This can result from small intestinal bacterial overgrowth, pancreatic exocrine insufficiency, obstruction of lymphatic vessels, bowel resection, or radiation therapy-induced intestinal lymphangiectasia (Andreyev et al., 2014).
    - (b) Bile acid malabsorption results from impaired absorption of bile acids in the terminal ileum (Fernandes & Andreyev, 2020).
  - (3) Small intestinal bacterial overgrowth can occur from alterations to function, motility, anatomy, metabolic, or immune disorders (Grace et al., 2013).
  - (4) Stool impaction (Bossi et al., 2018)
  - (5) Neutropenic enterocolitis (also called typhlitis) has a pathogenesis that is not entirely understood and is characterized by mucosal injury and neutropenia (Rodrigues et al., 2017).
  - (6) Excess use of laxatives
  - (7) Infection-related diarrhea (Brahmer et al., 2018)
    - (a) Bacterial infections: nontyphoidal *Salmonella*, *Sigella*, *Yersinia*, *Clostridium difficile*, *Escherichia coli*, *Campylobacter*
    - (b) Viral infections: norovirus, rotavirus, adenovirus, cytomegalovirus
    - (c) Parasitic infections: *Blastocystis*, *Cryptosporidium*, *Cyclospora cayetansensis*, *Entamoeba histolytica*, *Giardia lamblia*, *Cystoisospora belli*, *Sarcocystis hominis*, *Sarcocystis suihominis*, *Strongyloides stercoralis*
  - (8) Surgical resection (Bossi et al., 2018)
3. Incidence: The incidence of diarrhea varies greatly depending on the agents that are used. The specific agent, dose, schedule, and combination with other cancer therapies influence the severity of chemotherapy-induced diarrhea (McQuade et al., 2016; see Figure 15-6).
- a) Chemotherapy: Overall incidence may be as high as 80%; incidence of postchemotherapy chronic diarrhea may be as high as 49%. Regimens containing either irinotecan or 5-fluorouracil account for up to 80% of chemotherapy-induced diarrhea and one-third of patients experiencing grade 3–4 diarrhea (McQuade et al., 2016).
    - (1) 5-Fluorouracil: Diarrhea is more common with administration with leucovorin (up to 50%), and severity increases with bolus administration (Stein et al., 2010).
    - (2) Irinotecan
    - (3) Capecitabine
    - (4) Taxanes
      - (a) Cabazitaxel
      - (b) Docetaxel
      - (c) Paclitaxel
    - (5) Anthracyclines
  - b) Targeted therapy: Overall incidence is approximately 60% and is primarily associated with TKIs (Bossi et al., 2018; Pessi et al., 2014).
    - (1) Small molecule EGFR inhibitors
    - (2) Anti-EGFR monoclonal antibodies
      - (a) Cetuximab
      - (b) Panitumumab
    - (3) Phosphoinositide 3-kinase inhibitors (PI3K): Highest risk are idelalisib and duvelisib for diarrhea and colitis.
    - (4) Small molecule VEGF inhibitors
    - (5) BCR-ABL1 and KIT TKIs
    - (6) Cyclin-dependent kinase inhibitors (CDK): Highest rates are with abemaciclib, but they are typically low grade.
    - (7) Trastuzumab antibody–drug conjugates
    - (8) mTOR inhibitors
    - (9) Anaplastic lymphoma kinase (ALK) inhibitors: most commonly with ceritinib; rarely severe
    - (10) Mitogen-activated protein kinase (MAPK) inhibitors
    - (11) Bruton tyrosine kinase (BTK) inhibitors
    - (12) Poly(ADP-ribose) polymerase (PARP) inhibitors
  - c) Immunotherapy (Bossi et al., 2018; Brahmer et al., 2018; Dougan et al., 2020; Haanen et al., 2017; Puzanov et al., 2017; Thompson et al., 2019)
    - (1) Anti-CTLA-4 (up to 54% incidence): Higher incidence of diarrhea than PD-1/PD-L1 inhibitors; GI toxicity is the first immune-related adverse event leading to anti-CTLA-4 discontinuation.
    - (2) Anti-PD-1 drugs: Approximately 20% of patients on PD-L1 inhibitors will develop diarrhea of any grade, with severe toxicities much less common than anti-CTLA-4 agents.
4. Clinical manifestations
- a) Increase in frequency of bowel movements or loose consistency of stool



**FIGURE 15-6. Antineoplastics With High Risk for Diarrhea and Colitis**

| Antineoplastic Chemotherapies                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          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| <ul style="list-style-type: none"> <li>• Arsenic trioxide (Trisenox<sup>®</sup>; Teva Pharmaceuticals, 2020b)</li> <li>• Cabazitaxel (Jevtana<sup>®</sup>; Sanofi-Aventis U.S., 2021a)</li> <li>• Capecitabine (Xeloda<sup>®</sup>; Genentech, 2015)</li> <li>• Clofarabine (Clolar<sup>®</sup>; Sanofi-Aventis U.S., 2014)</li> <li>• Doxorubicin (Doxil<sup>®</sup>; Ortho-Biotech Products, 2007)</li> <li>• 5-Fluorouracil</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | <ul style="list-style-type: none"> <li>• Irinotecan (Camptosar<sup>®</sup>; Pfizer 2020a)</li> <li>• Ixabepilone (Ixempra<sup>®</sup>; Baxter Oncology, 2016)</li> <li>• Oxaliplatin (Eloxatin<sup>®</sup>; Sanofi-Aventis U.S., 2020a)</li> <li>• Paclitaxel (Taxol<sup>®</sup>; Bristol-Myers Squibb, 2011)</li> <li>• Paclitaxel protein bound (Abraxane<sup>®</sup>; Celgene, 2020)</li> <li>• Topotecan (Teva Pharmaceuticals; 2014)</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Targeted Therapies                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     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| <ul style="list-style-type: none"> <li>• ALK (anaplastic lymphoma kinase) inhibitor               <ul style="list-style-type: none"> <li>– Lorlatinib (Lorbrena<sup>®</sup>; Pfizer, 2021b)</li> </ul> </li> <li>• B-cell lymphoma inhibitor               <ul style="list-style-type: none"> <li>– Venetoclax (Venclexta<sup>®</sup>; Genentech, 2020e)</li> </ul> </li> <li>• BCR-ABL1 (breakpoint cluster-Abelson) inhibitors               <ul style="list-style-type: none"> <li>– Bosutinib (Bosulif<sup>®</sup>; Pfizer, 2021a)</li> <li>– Imatinib (Gleevec<sup>®</sup>; Novartis Pharmaceuticals, 2020a)</li> <li>– Nilotinib (Tasigna<sup>®</sup>; Novartis Pharmaceuticals, 2020d)</li> <li>– Ponatinib (Iclusig<sup>®</sup>; Ariad Pharmaceuticals &amp; Takeda Oncology, 2020)</li> </ul> </li> <li>• BRAF (B-type Raf kinase) inhibitor               <ul style="list-style-type: none"> <li>– Dabrafenib (Tafinlar<sup>®</sup>; Novartis Pharmaceuticals, 2021e)</li> </ul> </li> <li>• BTK (Bruton tyrosine kinase) inhibitors               <ul style="list-style-type: none"> <li>– Acalabrutinib (Calquence<sup>®</sup>; AstraZeneca Pharmaceuticals, 2019)</li> <li>– Ibrutinib (Imbruvica<sup>®</sup>; Pharmacyclics &amp; Janssen Biotech, 2020)</li> <li>– Zanubrutinib (Brukinsa<sup>®</sup>; BeiGene USA, 2019)</li> </ul> </li> <li>• CDK (cyclin-dependent kinase) inhibitors               <ul style="list-style-type: none"> <li>– Abemaciclib (Verzenio<sup>®</sup>; Eli Lilly and Company, 2020b)</li> <li>– Palbociclib (Ibrance<sup>®</sup>; Pfizer, 2019)</li> <li>– Ribociclib (Kisqali<sup>®</sup>; Novartis Pharmaceuticals, 2020b)</li> </ul> </li> <li>• EGFR (epidermal growth factor receptor) inhibitors               <ul style="list-style-type: none"> <li>– Afatinib (Gilotrif<sup>®</sup>; Boehringer Ingelheim Pharmaceuticals, 2019)</li> <li>– Dacomitinib (Vizimpro<sup>®</sup>; Pfizer, 2020f)</li> <li>– Erlotinib (Tarceva<sup>®</sup>; Genentech, 2016)</li> <li>– Gefitinib (Iressa<sup>®</sup>; AstraZeneca Pharmaceuticals, 2021a)</li> <li>– Infigratinib (Truseltiq<sup>®</sup>; QED Therapeutics, 2021)</li> <li>– Lapatinib (Tykerb<sup>®</sup>; Novartis Pharmaceuticals, 2020e)</li> <li>– Mobocertinib (Exkivity<sup>®</sup>; Takeda Oncology, 2021)</li> <li>– Osimertinib (Tagrisso<sup>®</sup>; AstraZeneca Pharmaceuticals, 2020b)</li> </ul> </li> <li>• FGFR (fibroblast growth factor receptor) inhibitors               <ul style="list-style-type: none"> <li>– Erdafitinib (Balversa<sup>®</sup>; Janssen Biotech, 2020a)</li> <li>– Pemigatinib (Pemazyre<sup>®</sup>; Incyte, 2021)</li> </ul> </li> <li>• HDAC (histone deacetylases) inhibitors               <ul style="list-style-type: none"> <li>– Belinostat (Beleodaq<sup>®</sup>; Acrotech Biopharma, 2020a)</li> <li>– Panobinostat (Farydak<sup>®</sup>; Novartis Pharmaceuticals, 2016)</li> <li>– Vorinostat (Zolinza<sup>®</sup>; Merck, 2020)</li> </ul> </li> <li>• Hedgehog inhibitors               <ul style="list-style-type: none"> <li>– Sonidegib (Odomzo<sup>®</sup>; Sun Pharmaceutical Industries, 2019)</li> <li>– Vismodegib (Erivedge<sup>®</sup>; Genentech, 2020a)</li> </ul> </li> <li>• HER2 (human epidermal growth factor receptor 2) inhibitor               <ul style="list-style-type: none"> <li>– Tucatinib (Tukysa<sup>®</sup>; Seattle Genetics, 2020)</li> </ul> </li> <li>• IDH1 (isocitrate dehydrogenase genes) inhibitors               <ul style="list-style-type: none"> <li>– Enasodenib (Idhifa<sup>®</sup>; Celgene, 2021b)</li> <li>– Ivosidenib (Tibsovo<sup>®</sup>; Seattle Genetics, 2021)</li> </ul> </li> <li>• JAK (Janus kinase) inhibitor               <ul style="list-style-type: none"> <li>– Fedratinib (Inrebic<sup>®</sup>; Celgene, 2019a)</li> </ul> </li> <li>• KIT (proto-oncogene) inhibitor               <ul style="list-style-type: none"> <li>– Ripretinib (Qinlock<sup>®</sup>; Deciphera Pharmaceuticals, 2021)</li> </ul> </li> </ul> | <ul style="list-style-type: none"> <li>• MEK (mitogen-activated extracellular signal regulated kinase) inhibitors               <ul style="list-style-type: none"> <li>– Binimetinib (Mektovi<sup>®</sup>; Array BioPharma, 2020)</li> <li>– Cobimetinib (Cotellic<sup>®</sup>; Genentech, 2018)</li> <li>– Selumetinib (Koselugo<sup>®</sup>; AstraZeneca Pharmaceuticals, 2021b)</li> </ul> </li> <li>• MET (mesenchymal epithelial transition) inhibitor               <ul style="list-style-type: none"> <li>– Tepotinib (Tepmetko<sup>®</sup>; EMD Serono, 2021)</li> </ul> </li> <li>• mTOR (mammalian target of rapamycin) inhibitors               <ul style="list-style-type: none"> <li>– Everolimus (Afinitor<sup>®</sup>, Afinitor Dispersz<sup>®</sup>; Novartis Pharmaceuticals, 2021a)</li> <li>– Temsirolimus (Torisel<sup>®</sup>; Pfizer, 2018)</li> </ul> </li> <li>• Multikinase inhibitors               <ul style="list-style-type: none"> <li>– Brigatinib (Alunbrig<sup>®</sup>; Takeda Oncology, 2020)</li> <li>– Cabozantinib (Cometriq<sup>®</sup>, Cabometyx<sup>®</sup>; Exelixis, 2020, 2021)</li> <li>– Ceritinib (Zykadia<sup>®</sup>; Novartis Pharmaceuticals, 2021f)</li> <li>– Dasatinib (Sprycel<sup>®</sup>; Bristol-Myers Squibb, 2021c)</li> <li>– Gilteritinib (Xospata<sup>®</sup>; Astellas Pharma, 2019)</li> <li>– Neratinib (Nerlynx<sup>®</sup>; Puma Biotechnology, 2021)</li> <li>– Pazopanib (Votrient<sup>®</sup>; Novartis Pharmaceuticals, 2020f)</li> <li>– Regorafenib (Stivarga<sup>®</sup>; Bayer HealthCare Pharmaceuticals, 2020)</li> <li>– Sorafenib (Nexavar<sup>®</sup>; Bayer HealthCare Pharmaceuticals, 2019)</li> <li>– Sunitinib (Sutent<sup>®</sup>; Pfizer, 2020d)</li> <li>– Umbralisib (Ukoniq<sup>™</sup>; TG Therapeutics, 2021)</li> <li>– Vandetanib (Caprelsa<sup>®</sup>; Sanofi Genzyme, 2020)</li> </ul> </li> <li>• PARP (poly [ADP-ribose] polymerase) inhibitors               <ul style="list-style-type: none"> <li>– Niraparib (Zejula<sup>®</sup>; GlaxoSmithKline, 2021b)</li> <li>– Olaparib (Lynparza<sup>®</sup>; AstraZeneca Pharmaceuticals, 2021c)</li> <li>– Rucaparib (Rubraca<sup>®</sup>; Clovis Oncology, 2020)</li> <li>– Talazoparib (Talzenna<sup>®</sup>; Pfizer, 2020e)</li> </ul> </li> <li>• PDGFR (platelet-derived growth factor receptor) inhibitor               <ul style="list-style-type: none"> <li>– Avapritinib (Ayvakit<sup>™</sup>; Blueprint Medicines, 2021a)</li> </ul> </li> <li>• PI3K (phosphoinositide 3-kinase) inhibitors               <ul style="list-style-type: none"> <li>– Abemaciclib (Verzenio<sup>®</sup>; Eli Lilly and Company, 2020b)</li> <li>– Alpelisib (Piqray<sup>®</sup>; Novartis Pharmaceuticals, 2019)</li> <li>– Copanlisib (Aliqopa<sup>®</sup>; Bayer HealthCare Pharmaceuticals, 2021a)</li> <li>– Duvelisib (Copiktra<sup>®</sup>; Verastem, 2019)</li> <li>– Idelalisib (Zydelig<sup>®</sup>; Gilead Sciences, 2020)</li> </ul> </li> <li>• Proteasome inhibitors               <ul style="list-style-type: none"> <li>– Bortezomib (Velcade<sup>®</sup>; Millennium Pharmaceuticals, 2019)</li> <li>– Carfilzomib (Kyprolis<sup>®</sup>; Onyx Pharmaceuticals, 2021)</li> <li>– Ixazomib (Ninlaro<sup>®</sup>; Millennium Pharmaceuticals, 2021)</li> </ul> </li> <li>• RAS (rat sarcoma virus) inhibitor               <ul style="list-style-type: none"> <li>– Sotorasaib (Lumakras<sup>®</sup>; Amgen, 2021a)</li> </ul> </li> <li>• RET (rearranged during transfection) inhibitors               <ul style="list-style-type: none"> <li>– Pralsetinib (Gavreto<sup>™</sup>; Blueprint Medicines, 2021b)</li> <li>– Selpercatinib (Retevmo<sup>™</sup>; Eli Lilly and Company, 2021)</li> </ul> </li> <li>• TPO (thrombopoietin) receptor agonist               <ul style="list-style-type: none"> <li>– Eltrombopag (Promacta<sup>®</sup>; Novartis Pharmaceuticals, 2021b)</li> </ul> </li> <li>• TRK (tropomyosin receptor kinase) inhibitors               <ul style="list-style-type: none"> <li>– Entrectinib (Rozlytrek<sup>®</sup>; Genentech, 2019b)</li> <li>– Larotrectinib (Vitrakvi<sup>®</sup>; Bayer HealthCare Pharmaceuticals, 2021b)</li> </ul> </li> </ul> |

(Continued on next page)

**FIGURE 15-6. Antineoplastics With High Risk for Diarrhea and Colitis (Continued)**

| Targeted Therapies (Cont.)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             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| <ul style="list-style-type: none"> <li>• VEGFR (vascular endothelial growth factor receptor) inhibitors               <ul style="list-style-type: none"> <li>– Axiyinib (Inlyta<sup>®</sup>; Pfizer, 2020c)</li> <li>– Lenvatinib (Lenvima<sup>®</sup>; Eisai, 2021)</li> <li>– Tivozanob (Fotivda<sup>®</sup>; AVEO Pharmaceuticals, 2021)</li> <li>– Ziv-aflibercept (Zaltrap<sup>®</sup>; Sanofi-Aventis U.S., 2020b)</li> </ul> </li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | <ul style="list-style-type: none"> <li>• XPO (exportin) inhibitor               <ul style="list-style-type: none"> <li>– Selinexor (Xpovio<sup>®</sup>; Karyopharm Therapeutics, 2021)</li> </ul> </li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Immunotherapies                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        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                                                                                                                                                                                                                          |
| <ul style="list-style-type: none"> <li>• Chimeric antigen receptor T-cell therapy               <ul style="list-style-type: none"> <li>– Axicabtagene ciloleucel (Yescarta<sup>®</sup>; Kite Pharma, 2021b)</li> <li>– Brexucabtagene autoleucel (Tecartus<sup>®</sup>; Kite Pharma, 2021a)</li> <li>– Idecabtagene vicleucel (Abecma<sup>®</sup>; Celgene, 2021a)</li> <li>– Tisagenlecleucel (Kymriah<sup>®</sup>; Novartis Pharmaceuticals, 2020c)</li> <li>– Lisocabtagene maraleucel (Breyanzi<sup>®</sup>; Bristol-Myers Squibb, 2021a)</li> </ul> </li> <li>• Antibody-drug conjugates               <ul style="list-style-type: none"> <li>– Enfortumab vedotin-efv (Padcev<sup>™</sup>; Astellas Pharma, 2021)</li> <li>– Fam-trastuzumab deruxtecan-nxki (Enhertu<sup>®</sup>; Daiichi Sankyo, 2021)</li> <li>– Gemtuzumab ozogamicin (Mylotarg<sup>™</sup>; Wyeth Pharmaceuticals, 2020)</li> <li>– Polatuzumab vedotin-piiq (Polivy<sup>™</sup>; Genentech, 2020d)</li> <li>– Sacituzumab govitecan-hziy (Trodelyv<sup>™</sup>; Immunomedics, 2020)</li> </ul> </li> <li>• Immunomodulators               <ul style="list-style-type: none"> <li>– Lenalidomide (Revlimid<sup>®</sup>; Celgene, 2021d)</li> <li>– Pomalidomide (Pomalyst<sup>®</sup>; Celgene, 2021c)</li> </ul> </li> <li>• Monoclonal antibodies               <ul style="list-style-type: none"> <li>– Bevacizumab (Avastin<sup>®</sup>; Genentech, 2021b)</li> <li>– Bevacizumab-awwb (Mvasi<sup>®</sup>; Amgen, 2021b)</li> <li>– Bevacizumab-bvzr (Zirabev<sup>™</sup>; Pfizer, 2021e)</li> <li>– Cetuximab (Erbix<sup>®</sup>; Eli Lilly and Company, 2020a)</li> <li>– Daratumumab (anti-CD38 antibody; Darzalex<sup>®</sup>; Janssen Biotech, 2020b)</li> <li>– Daratumumab and hyaluronidase-fihj (Darzalex Faspro<sup>™</sup>; Janssen Biotech, 2020c)</li> <li>– Elotuzumab (Empliciti<sup>®</sup>; Bristol-Myers Squibb, 2019)</li> <li>– Isatuximab-irfc (Sarclisa<sup>®</sup>; Sanofi-Aventis U.S., 2021b)</li> <li>– Margetuximab-cmkb (Margenza<sup>™</sup>; MacroGenics, 2020)</li> <li>– Mogamulizumab-kpkc (Poteligeo<sup>®</sup>; Kyowa Kirin, 2018)</li> <li>– Naxitamab-gqgk (Danyelza<sup>®</sup>; Y-mAbs Therapeutics, 2020)</li> <li>– Panitumumab (Vectibix<sup>®</sup>; Amgen, 2015)</li> <li>– Pertuzumab (Perjeta<sup>®</sup>; Genentech, 2021d)</li> <li>– Pertuzumab, trastuzumab, and hyaluronidase-zzxf (Phesgo<sup>™</sup>; Genentech, 2020c)</li> <li>– Rituximab and hyaluronidase (Rituxan Hycela<sup>®</sup>; Genentech, 2021e)</li> <li>– Tafasitamab-cxix (Monjuvi<sup>®</sup>; MorphoSys, 2020)</li> <li>– Trastuzumab (Herceptin<sup>®</sup>; Genentech, 2021c)</li> <li>– Trastuzumab-pkrb (Herzuma<sup>®</sup>; Teva Pharmaceuticals, 2019b)</li> <li>– Trastuzumab and hyaluronidase-oysk (Herceptin Hylecta<sup>™</sup>; Genentech, 2019a)</li> </ul> </li> </ul> | <ul style="list-style-type: none"> <li>• Radioimmune conjugate               <ul style="list-style-type: none"> <li>– <sup>90</sup>Y-ibritumomab tiuxetan (Zevalin<sup>®</sup>; Acrotech Biopharma, 2019)</li> </ul> </li> <li>• Checkpoint inhibitors               <ul style="list-style-type: none"> <li>– Anti-PD-L1 (programmed cell death-ligand 1)                   <ul style="list-style-type: none"> <li>* Avelumab (Bavencio<sup>®</sup>; EMD Serono, 2020)</li> <li>* Cemiplimab-rwlc (Libtayo<sup>®</sup>; Regeneron, 2021)</li> <li>* Dostarlimab-gxly (Jemperli<sup>®</sup>; GlaxoSmithKline, 2021a)</li> <li>* Durvalumab (Imfinzi<sup>®</sup>; AstraZeneca Pharmaceuticals, 2020a)</li> <li>* Nivolumab (Opdivo<sup>®</sup>; Bristol-Myers Squibb, 2021b)</li> <li>* Pembrolizumab (Keytruda<sup>®</sup>; Merck, 2021)</li> </ul> </li> <li>– Anti-CTLA-4 (cytotoxic T-lymphocyte antigen 4)                   <ul style="list-style-type: none"> <li>* Ipilimumab (Yervoy<sup>®</sup>; Bristol-Myers Squibb, 2021d)</li> </ul> </li> </ul> </li> <li>• Cytokines               <ul style="list-style-type: none"> <li>– Growth factors                   <ul style="list-style-type: none"> <li>* Darbepoetin (Aranesp<sup>®</sup>; Amgen, 2019)</li> <li>* Filgrastim (Neupogen<sup>®</sup>; Amgen, 2021c)</li> <li>* Filgrastim-aafi (Nivestym<sup>®</sup>; Pfizer, 2021c)</li> <li>* Filgrastim-sndz (Zarxio<sup>®</sup>; Sandoz, 2021)</li> <li>* Tbo-filgrastim (Granix<sup>®</sup>; Teva Pharmaceuticals, 2019a)</li> <li>* Sargramostim (GM-CSF [granulocyte macrophage-colony-stimulating factor]; Leukine<sup>®</sup>; Partner Therapeutics, 2018)</li> </ul> </li> <li>– Interferons                   <ul style="list-style-type: none"> <li>* Interferon alfa-2b (Intron<sup>®</sup> A; Merck, 2019a)</li> <li>* Interferon gamma (Actimmune<sup>®</sup>; Horizon Therapeutics, 2021)</li> </ul> </li> <li>– Interleukins                   <ul style="list-style-type: none"> <li>* Aldesleukin (Proleukin<sup>®</sup>; Clinigen, 2019)</li> </ul> </li> </ul> </li> <li>• Miscellaneous               <ul style="list-style-type: none"> <li>– Hematopoietic stem cell mobilizers                   <ul style="list-style-type: none"> <li>* Plerixafor (Mozobil<sup>®</sup>; Genzyme, 2020)</li> </ul> </li> <li>– Erythroid maturation agent                   <ul style="list-style-type: none"> <li>* Luspatercept-aamt (Reblozyl<sup>®</sup>; Celgene, 2019b)</li> </ul> </li> </ul> </li> </ul> |

- b) Gas or abdominal cramping
  - c) Clinical findings indicating dehydration
    - (1) Decreased skin turgor
    - (2) Dry mucous membranes
    - (3) Decreased urine output
    - (4) Laboratory findings
      - (a) Elevated serum creatinine
      - (b) Hypokalemia
      - (c) Metabolic acidosis
      - (d) Hyponatremia or hypernatremia
    - (5) Signs of infection (e.g., fever) (Andreyev et al., 2014)
  - d) Diarrhea can contribute to numerous sequelae, including dehydration, fever, malnutrition, sepsis, frank bleeding, moderate to severe cramping, renal insufficiency, cardiac dysfunction, and severe electrolyte imbalance. It can impair quality of life, cause treatment delays, force drug dose reductions and discontinuation, and even cause death (Andreyev et al., 2014; Koselke & Kraft, 2012).
    - (1) Additional sequelae may include perianal skin breakdown, discomfort, or infection; reduced absorption of oral medications; anxiety; and exhaustion.
    - (2) Immune-mediated colitis is characterized by abdominal pain, rectal or mucosal bleeding, and large bowel inflammation. It can progress to intestinal colitis and possibly death (Spain et al., 2016).
5. Risk factors
- a) Disease related (NCI, 2022b)
    - (1) Carcinoid syndrome
    - (2) Colon cancer
    - (3) Lymphoma
    - (4) Medullary carcinoma of the thyroid
    - (5) Pancreatic cancer
    - (6) Pheochromocytoma
  - b) Treatment related
    - (1) Chemotherapy: 5-fluorouracil, irinotecan, capecitabine, taxanes, anthracyclines, platinum salts (Bossi et al., 2018)
    - (2) Targeted therapy: anti-EGFR, anti-HER2, anti-BRAF, anti-MEK, anti-MEL4/ALK, anti-VEGF, TKIs, anti-mTOR, anti-CDK4/6, anti-PARP (Bossi et al., 2018)
    - (3) Immunotherapy: anti-CTLA-4, anti-PD-1/PD-L1 (Thompson et al., 2019)
    - (4) Radiation therapy: Monotherapy or combination radiation therapy, particularly to the pelvis, abdomen, or lower thoracic and lumbar spine, can lead to the destruction of the cells of the lumen of the bowel and can be acute or chronic toxicity (NCI, 2022b).
- (5) Surgery: Manipulation of the bowel during surgery may cause diarrhea or ileus. Procedures associated with higher risks of diarrhea include celiac plexus block, cholecystectomy, esophagogastrectomy, gastrectomy, pancreatic duodenectomy, intestinal resection, and vagotomy (NCI, 2022b).
  - (6) Other pharmacologic agents: antibiotics, magnesium-containing antacids, anti-hypertensives, colchicine, digoxin, iron, lactulose, laxatives, methyldopa, metoclopramide, misoprostol, potassium supplements, propranolol, theophylline (NCI, 2022b)
- c) Acute or chronic conditions (NCI, 2022b)
    - (1) Immunosuppression
    - (2) Infection related to mucositis and neutropenia (e.g., infection with rotavirus, *E. coli*, *Shigella*, *Salmonella*, *Giardia*, or *C. difficile*)
    - (3) Graft-versus-host disease
    - (4) Diabetes, hyperthyroidism, inflammatory bowel disease (e.g., Crohn disease, diverticulitis, gastroenteritis, HIV/AIDS, ulcerative colitis), obstruction (tumor related)
    - (5) Malabsorption, partial bowel obstruction, bowel edema, motility disruption
  - d) Behavioral and psychosocial (NCI, 2022b)
    - (1) Anxiety and stress
    - (2) Dietary causes (e.g., lactose intolerance; ingestion of caffeine, alcohol, or spicy or fatty foods; use of hyperosmotic dietary supplements)
6. Assessment: Timely and accurate assessment is critical to managing diarrhea and preventing severe sequelae, including death (NCI, 2022b).
- a) Assessment tools
    - (1) The *Common Terminology Criteria for Adverse Events* is the current standard for assessing and grading treatment-related toxicities, including diarrhea (Bossi et al., 2018; NCI CTEP, 2017). This does not consider volume, duration, social impact, or rectal urgency (Fernandes & Andreyev, 2020; see Figure 15-7).
    - (2) Bristol Stool Scale (Fernandes & Andreyev, 2020)
    - (3) Gastrointestinal Symptom Rating Scale (Fernandes & Andreyev, 2020)
    - (4) ALERT-B screening tool (Fernandes & Andreyev, 2020)

**FIGURE 15-7.** Evidence-Based Recommendations for the Management of Cancer Treatment–Induced Diarrhea

Assessment and Evaluation

History

- Physiologic history of gastrointestinal disturbances (e.g., baseline, treatment, and disease related)
- Current treatment type
- Duration, volume, consistency, and frequency of diarrhea
- Confounding factors (e.g., fever, orthostatic hypotension, abdominal pain or cramping, weakness)
- Symptom interference with quality of life and function

Physical assessment: abdominal assessment (e.g., visual assessment, auscultation for bowel sounds, palpitation, percussion as appropriate)

Laboratory assessment: Complete blood count, electrolytes, stool workup (e.g., presence of blood, fecal leukocytes, infectious sources), lactoferrin, and fecal calprotectin testing may be indicated at baseline and every 3 weeks during treatment with anti-programmed cell death protein 1 checkpoint inhibitors.

Common Terminology Criteria for Adverse Events Grading for Diarrhea

| Grade 1                                                                                           | Grade 2                                                                                                                                                 | Grade 3                                                                                                                                                                       | Grade 4                                                      | Grade 5 |
|---------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|---------|
| Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline | Increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental activities of daily living | Increase of ≥ 7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care activities of daily living | Life-threatening consequences; urgent intervention indicated | Death   |

Classification

Uncomplicated

- Grade 1–2 toxicity
- No additional signs or symptoms
- May be managed with nonpharmacologic approaches, including dietary changes and increased oral hydration to 3–4 L of water daily
- May also introduce pharmacologic measures

Complicated

- Grade 3–4 toxicity
- Grade 1–2 toxicity with ≥ 1 complicating symptoms (e.g., cramping, nausea, vomiting, fever, bleeding, dehydration, sepsis, neutropenia, decreased performance status)
- Should be managed in the hospital with IV fluids, electrolyte replacement, and pharmacologic measures

Management by Treatment Type

Chemotherapy and Targeted Therapy

Uncomplicated

- Decrease or delay chemotherapy or targeted therapy.
- Initiate oral hydration and electrolyte replacement, if indicated.
- Initiate loperamide.
- Consider dietary modifications.
- Initiate IV fluids if patients are unable to tolerate oral fluids.
- Notify treating physician.

Complicated

- Discontinuation (temporarily or permanently) of causative agent may be necessary.
- Consider anticholinergic agents.
- Transition to or escalate dosing of octreotide.
- Continue or initiate antibiotic therapy if infection related.
- Consider stool evaluation.
- Evaluate labs (e.g., complete blood count, electrolytes) daily.
- Initiate or continue dietary modifications.

Assessment for Symptom Resolution

- Chemotherapy and targeted therapy: Assess diarrhea every 12–24 hours and escalate care as required in the presence of increased grading or persistent diarrhea; discontinue loperamide after 12 hours without diarrhea.
- Immunotherapy: Assess diarrhea every 12–24 hours; taper corticosteroids over 4–6 weeks before resuming. When symptoms improve to grade 1 or better, treatment may be restarted in the presence of low-dose steroids after evaluation of risks and benefits.
- Regardless of treatment, consider use of a patient journal to document stool frequency and characteristics in the ambulatory setting.

See Table 15-8 for Common Terminology Criteria for Adverse Events Grading of Colitis.

Note. Based on information from Bossi et al., 2018; Brahmer et al., 2018; National Cancer Institute, 2022b; National Cancer Institute Cancer Therapy Evaluation Program, 2017; National Comprehensive Cancer Network, 2022a; Puzanov et al., 2017; Thompson et al., 2019

## b) Assessment elements (Andreyev et al., 2014)

## (1) History

- (a) Assess patients for concerning symptoms, which include abdominal cramps or nausea not responsive to pharmacologic management, inability to eat, increased fatigue, dizziness, chest pain, vomiting, reduced urine output secondary to dehydration, fever (higher than 38.5°C), GI bleed, changes in mental status, and previous admission for diarrhea-related complications.
- (b) Include a diet history to evaluate for items that could contribute to diarrhea (e.g., irritating foods, alcohol, coffee, fiber, fruit, lactose-containing foods or fluids, sorbitol-based gum, candy, herbal teas that may contain laxatives), as well as history or new onset of food or lactose intolerance or allergies.
- (c) Assess stool quality and characteristics, including duration, continence, changes in bowel patterns, frequency, consistency, volume, odor, and visible presence of blood.
- (d) Evaluate current or recent medications, including antacids (especially those containing magnesium), antiarrhythmics, antibiotics, antihypertensives, caffeine, diuretics, laxatives or stool softeners, magnesium oxide, nonsteroidal anti-inflammatory drugs, potassium or calcium supplements, pro-motility agents (e.g., metoclopramide), proton pump inhibitors, and theophylline.
- (e) Evaluate other confounding factors, including travel history (outside the United States), use of alternative therapies (e.g., dietary supplements, herbal remedies), and opioid withdrawal.
- (f) Other etiologies of diarrhea include abdominopelvic radiation, prior intestinal surgeries, malabsorption, stool impaction.
- (g) The presence of ileostomy should be evaluated. Normal output averages 600–800 ml daily (Livia de Oliveira et al., 2018). These patients are generally on a baseline regimen of loperamide and should be assessed for

adherence to this regimen and oral intake.

## (2) Physical assessment

- (a) Vital signs
- (b) Weight (with attention to significant weight gain or loss)
- (c) Physical examination, with particular attention to the GI system (e.g., visual inspection; palpation and auscultation of the abdomen with attention to guarding and rebound tenderness; assessment for fecal impaction, including in patients with neutropenia, unless such an examination would cause severe rectal pain)
- (d) Alterations in skin integrity, mainly focused on the perianal area
- (e) Evaluation for signs and symptoms of dehydration, including hypotension, delayed capillary refill, and reduced skin turgor

## (3) Laboratory assessment (Bossi et al., 2018; NCCN, 2022a)

- (a) Stool sample for consistency, presence of blood, and infectious sources: Conduct *C. difficile*, *Salmonella*, *E. coli*, or *Campylobacter* testing. Consider testing for rotavirus and norovirus in the winter and bacterial and parasite cultures if travel would put patients at risk.
- (b) Serum chemistries for electrolyte imbalance, specifically potassium
- (c) Albumin levels, which may be decreased with diarrhea
- (d) Complete blood count to determine if neutropenia or infection is present
- (e) Acid–base balance and lactate concentrations in the presence of hypotension and tachycardia
- (f) Urinalysis
- (g) Biopsy of ulcerations to evaluate for viral infection, particularly cytomegalovirus
- (h) Blood cultures can be performed to detect bloodstream infection in patients with severe, persistent diarrhea accompanied by neutropenia, fever, or blood in the stool.

## (4) Radiographic and endoscopic assessment (Bossi et al., 2018)

- (a) CT scan of the abdomen to evaluate for enterocolitis, perforation, abscess, bowel ischemia, and pancreatitis
- (b) Endoscopy

- (c) Ultrasound to assess peristalsis and intestinal wall thickening
  - (d) Colonoscopy is generally not recommended for patients with suspected neutropenia.
7. Collaborative management
- a) Fluid resuscitation: Rapid fluid resuscitation is unnecessary in patients with mild hypovolemia. The ideal rate of fluid intake should exceed the rate of losses. Urine output should be met and sustained at a minimum of 0.5 ml/kg/hr (Bossi et al., 2018).
    - (1) Oral: Daily fluid intake of 2–4 L of water is recommended, in some cases with the addition of salt and sugar (Bossi et al., 2018; Pessi et al., 2014).
    - (2) IV: Fluid bolus, preferably using normal saline (never hypotonic solutions such as 5% dextrose in water), should be implemented to evaluate blood plasma volume increases. If hemodynamic stability is not achieved, further evaluation from an intensivist or nephrologist should be sought (Andreyev et al., 2014).
  - b) Electrolyte repletion
    - (1) Hypokalemia: potassium less than 3.5 mEq/L
    - (2) Hypomagnesemia: less than 0.4 mmol/L or, in symptomatic patients, less than 0.4–0.7 mmol/L
    - (3) Hypocalcemia: adjusted calcium concentration less than 2.2 mmol/L
    - (4) Hypophosphataemia: If severe (less than 0.3 mmol/L) or moderate (0.3–0.6 mmol/L), consider repletion; hypomagnesemia and hypocalcemia might predispose patients to hypophosphatemia.
  - c) Pharmacologic management
    - (1) Chemotherapy- and targeted therapy-induced diarrhea
      - (a) Loperamide is a nonanalgesic agonist that decreases intestinal motility through activity on the mu-opioid receptor in the mesenteric plexus (McQuade et al., 2016).
        - i. The first dose is 4 mg; each additional dose is 2 mg. Patients can take this medication every two to four hours or after each unformed stool, taken 30 minutes before food if possible (Andreyev et al., 2014; Thorpe et al., 2017).
        - ii. Maximum dosing is 16 mg daily (Bossi et al., 2018).
      - (b) Octreotide is a synthetic somatostatin analog that increases intestinal transit time by inhibiting gut hormones (McQuade et al., 2016).
        - i. Starting dose is generally 100–150 mcg three times daily but can be rapidly titrated as needed to 500 mcg three times daily.
        - ii. It may be administered via IV or subcutaneous injection.
        - iii. Octreotide may be effective in patients refractory to loperamide (Andreyev et al., 2014; Bossi et al., 2018; Thorpe et al., 2017).
      - (c) Tincture of opium decreases intestinal motility through activity on the mu-opioid receptors; it contains 10 mg/ml of morphine (McQuade et al., 2016).
        - i. Dosing is 10–15 drops per three to four hours. Evidence is limited, specifically in chemotherapy- and targeted therapy-induced diarrhea; however, it may be used as second-line therapy (Koselke & Kraft, 2012).
        - ii. Monitor for side effects, including nausea and vomiting (most common), painful urination, allergic reaction, seizure, abdominal pain, constipation, and potential for respiratory depression (McQuade et al., 2016).
      - (d) Evidence is mixed regarding using steroids alone or in combination with loperamide (Shumar et al., 2019).
      - (e) Antibiotics are only indicated for patients with suspected infectious etiology that display clinical manifestations, such as fever, hypotension, and neutropenia (Bossi et al., 2018; Koselke & Kraft, 2012).
      - (f) Prophylactic atropine
        - i. Irinotecan is a chemotherapy agent that can cause acute diarrhea (during or immediately after administration) or delayed diarrhea.
        - ii. Immediate-onset diarrhea is caused by acute cholinergic properties and often is accom-



- panied by other symptoms, including abdominal cramping, rhinitis, lacrimation, and salivation.
- iii. The mean duration of symptoms is 30 minutes, and they usually respond rapidly to atropine.
  - iv. Delayed diarrhea is defined as diarrhea occurring more than 24 hours after administration of irinotecan and is commonly treated with loperamide (NCCN, 2022a).
  - v. Prophylactic atropine may be considered (unless clinically contraindicated) for patients who experience cholinergic symptoms (Bossi et al., 2018; see Table 15-5).
- (g) Uridine triacetate is used for early-onset severe toxicity of 5-fluorouracil/capecitabine-induced diarrhea within 96 hours following agent administration. The recommended dose is 10 g orally every six hours for 20 doses (Bossi et al., 2018).
- (2) Immune-mediated diarrhea (Spain et al., 2016): Refer to section D for a full review of colitis management.
- d) Other management strategies
- (1) For severe immune-mediated colitis with resulting diarrhea, colectomy may be appropriate in select cases (Spain et al., 2016).
  - (2) Dietary modifications, including a bland diet, may be implemented (Schmidt-Hieber et al., 2017; Thorpe et al., 2017).
  - (3) Evidence suggests the potential efficacy of probiotics in reducing antibiotic-associated diarrhea; however, more studies are needed to evaluate safety (Bowen et al., 2019).
  - (4) Skin barriers should be used to help prevent skin breakdown
- e) Interventions by category
- (1) Uncomplicated
    - (a) Oral hydration and electrolyte replacement
    - (b) Antidiarrheal medication
      - i. Administer antidiarrheal medication as appropriate once an infection has been ruled out.

**TABLE 15-5.** Common Antidiarrheal Medications

| Classification      | Mechanism of Action                                                                                 | Drug                                                                      | Route, Dose, and Schedule for Adult Patients <sup>a</sup>                                                      | Side Effects <sup>a</sup>                                                         | Nursing Considerations <sup>a</sup>                                                                                                                                                                                                                                                                                                |
|---------------------|-----------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Anticholinergics    | Antagonist of acetylcholine                                                                         | Atropine                                                                  | Used for early-onset cholinergic diarrhea (e.g., irinotecan induced), 0.25–1 mg IV or SC                       | Dry mouth, blurred vision, photophobia, constipation, xerostomia, tachyarrhythmia | Antacids interfere with absorption of the drug. The drug is contraindicated in patients with closed-angle glaucoma. (Intas Pharmaceuticals, 2019)                                                                                                                                                                                  |
| Antimotility agents | Slows gastrointestinal transit time and promotes reabsorption of water from bowel; anti-peristaltic | Diphenoxylate hydrochloride with atropine sulfate (Lomotil <sup>®</sup> ) | Individualize dosage. Initial dose is 10 mg followed by 5 mg PO four times daily; maximum dose is 20 mg daily. | Dry mouth, urinary retention, confusion, sedation, restlessness                   | Bacterial diarrhea should also be managed with the appropriate antimicrobial therapy. The drug is contraindicated for the treatment of diarrhea secondary to pseudomembranous colitis. In patients with advanced liver disease, the drug may precipitate hepatic coma. Do not use in children younger than 2 years. (Pfizer, 2017) |

(Continued on next page)



**TABLE 15-5.** Common Antidiarrheal Medications (*Continued*)

| Classification                       | Mechanism of Action                                                                                                     | Drug                      | Route, Dose, and Schedule for Adult Patients <sup>a</sup>                                                                                                                                         | Side Effects <sup>a</sup>                                                                                                | Nursing Considerations <sup>a</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|--------------------------------------|-------------------------------------------------------------------------------------------------------------------------|---------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Antimotility agents ( <i>Cont.</i> ) |                                                                                                                         | Loperamide (Imodium® A-D) | Initial dose is 4 mg PO followed by 2 mg PO after each unformed stool; do not exceed 16 mg daily.<br>Exception: Doses are higher for late-onset irinotecan-induced diarrhea (2 mg every 2 hours). | Constipation, fatigue, urinary retention, drowsiness, dizziness                                                          | Bacterial diarrhea should also be managed with the appropriate antimicrobial therapy.<br>Do not use in children younger than 2 years. (Janssen Biotech, 1998)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Somatostatin analogs                 | Inhibits growth hormone, glucagon, and insulin; prolongs intestinal transit time; increases sodium and water absorption | Octreotide (Sandostatin®) | 100–150 mcg SC or IV three times daily<br>Doses may be escalated to 500 mcg SC or IV three times daily or by continuous IV infusion 25–50 mcg/hr.                                                 | Abdominal discomfort, flatulence, constipation, diarrhea, nausea, dizziness, headache, cardiac dysrhythmias, bradycardia | The drug may interact with insulin, oral hypoglycemic medications, beta-blockers, and calcium channel blockers. Insulin requirements may be decreased.<br>Monitor for hyperglycemia and hypoglycemia.<br>The drug may decrease levels of cyclosporine when given concurrently.<br>The drug may increase risk of developing gallstones.<br>The drug is recommended after failure of loperamide or in patients with complicated diarrhea. Complicated diarrhea is defined as involving abdominal cramping, nausea and vomiting, fever, sepsis, neutropenia, or bleeding.<br>Sandostatin LAR Depot is under investigation for the treatment of chemotherapy-induced diarrhea. (Novartis Pharmaceuticals, 2021d) |

<sup>a</sup> Consult product information for complete list of contraindications, drug interactions, and dosage ranges.

IV—intravenous; PO—oral; SC—subcutaneous

- ii. This will reduce stool frequency, volume, and peristalsis.
- iii. Mistakenly using an antidiarrheal to treat diarrhea caused by infection can intensify diarrhea severity and infectious complications.

- (c) Dose reduction or discontinuation of chemotherapy if diarrhea is chemotherapy induced
- (d) Diet modification
- (2) Complicated
  - (a) Inpatient hospitalization, including intensive care for grade 4

- (b) IV fluids if patients cannot tolerate oral hydration
  - (c) Initiation or continuation of loperamide
  - (d) Introduction or continuation of bland diet or clear liquids
  - (e) Consideration of somatostatin
  - (f) Consideration of antibiotic therapy if diarrhea is infection related
  - (g) Delay or discontinuation of chemotherapy if diarrhea is chemotherapy induced
  - (h) Consideration of corticosteroids, infliximab, probiotics, or dose reduction or discontinuation of immunotherapy agent for immune-related diarrhea
  - (i) Withholding of immunotherapy agent if diarrhea is immune mediated
  - (j) IV electrolyte supplementation
  - (k) For graft-versus-host disease–related diarrhea, steroids, loperamide, and consideration of IV nutrition (Lieow & Christensen, 2014)
8. Patient and family education (Muehlbauer et al., 2009)
- a) Discuss treatment-related risks and diarrhea manifestations with patients and caregivers at the outset of treatment, using visual aids, such as the Bristol Stool Scale, as appropriate (Andreyev et al., 2014).
  - b) Educate patients to be aware of their baseline bowel functioning, monitor for changes in bowel habits, and report changes to their provider.
  - c) Start antidiarrheal medications at the specified time. Antidiarrheal medications should be provided with specific chemotherapy agents so that patients can self-administer at the onset.
  - d) Instruct patients on dietary recommendations and fluid intake.
    - (1) Avoid foods high in insoluble fiber (e.g., raw fruits and vegetables), greasy or fried foods, lactose, skins, seeds, legumes, caffeine, alcohol, and hyperosmotic liquids. These may be stimulating or irritating to the GI tract.
    - (2) Include foods high in soluble fiber or pectin in their diets and low insoluble fiber foods, such as rice noodles, bananas, white toast, skinned turkey or chicken, fish, and mashed potatoes.
    - (3) Maintain fluid intake by drinking 8–10 large glasses each day of clear fluids (e.g., bouillon; weak, tepid decaffeinated tea; gelatin; sports drinks). Water alone lacks the needed electrolytes and vitamins. Carbonated and caffeinated drinks contain relatively few electrolytes and may worsen diarrhea. Fluids with glucose are useful because glucose absorption drives sodium and water back into the body.
  - (4) Limit the use of sugar-free candies or gum made with sugar alcohol (sorbitol), which can cause diarrhea (NCI, 2022b).
  - (5) Eat food at room temperature if not tolerated otherwise. Hot and cold foods may aggravate diarrhea.
  - (6) Limit or avoid milk and other dairy products.
  - (7) Avoid hyperosmotic supplements (e.g., Ensure®), which can contribute to the production of loose, high-volume stools.
  - e) Instruct patients and families on skin care.
    - (1) Clean the rectal area with mild soap and water after each bowel movement, rinsing well and patting dry with a soft towel. Cleansing decreases the risk of infection and skin irritation.
    - (2) Apply moisture-barrier ointment to protect perianal skin.
    - (3) Take warm sitz baths to relieve pain related to perianal inflammation. Anesthetic creams or sprays may help to relieve pain related to inflammation.
  - f) Educate patients and families on symptoms to report.
    - (1) Understand when diarrhea can be self-managed and when to seek help.
    - (2) Report excessive thirst, fever, dizziness or light-headedness, palpitations, rectal spasms, excessive cramping, watery or bloody stools, and continued diarrhea despite antidiarrheal treatment. These symptoms can be life threatening.
- D. Colitis
1. Overview: Colitis is a general term for a disorder characterized by the inflammation of the colon (NCI CTEP, 2017). Colitis has multiple causes and, therefore, slightly different definitions based on the causative agent.
    - a) Neutropenic enterocolitis (also called typhlitis): Though the etiology is not fully understood, neutropenic enterocolitis generally results from neutropenia and damage to the bowel mucosa from chemotherapy. Neutropenic enterocolitis can be life threatening (Nesher & Rolston, 2012; Palmore et al., 2019; Rodrigues et al., 2017).
      - (1) Severe neutropenia (absolute neutrophil count less than 500/mm<sup>3</sup>) decreases

- the immune response against local tissue invasion by intestinal microbes.
- (2) Mucosal injury predisposes the colon to distension and necrosis (Rodrigues et al., 2017).
  - (3) Mucosal motility can be altered, making the colon more vulnerable to bacterial invasion and overgrowth (Rodrigues et al., 2017).
  - (4) Multiple proinflammatory mediators inside the intestinal lumen cause increased mucosal permeability (Nesher & Rolston, 2012).
  - (5) The cause is frequently polymicrobial and includes bacterial and fungal species, such as *C. difficile* or *Candida albicans* (Nesher & Rolston, 2012; Palmore et al., 2019).
- b) *C. difficile* colitis (Neemann & Freifeld, 2017)
- (1) *C. difficile* is a gram-positive, spore-forming, anaerobic rod transmitted via the fecal-oral route.
  - (2) Pathogenesis
    - (a) Disruption of the normal microbiome flora
    - (b) Colonization with *C. difficile* toxigenic strain
    - (c) Activation of *C. difficile* genes to produce cytotoxin proteins
    - (d) Mucosal damage causing inflammation
- c) Immune-mediated colitis: Symptoms relate to diarrhea, but it has a clinically distinct diagnosis, with accompanying abdominal pain and radiographic or endoscopic findings of colonic inflammation. Inflammation in the colon is the most common GI immune-related adverse event related to immunotherapy (Dougan et al., 2020).
- (1) Anti-CTLA-4 monoclonal antibody (e.g., ipilimumab): Blockade of CTLA-4 leads to more frequent adverse events than other categories of immunotherapies (Dougan et al., 2020).
    - (a) Fully humanized monoclonal antibody (immunoglobulin G1) against CTLA-4 that promotes antitumor T-cell immunity
    - (b) Causes apoptosis of activated T cells, which negatively regulates T-cell activation
    - (c) Mechanism of action (Barina et al., 2016)
      - i. CTLA-4 monoclonal antibodies suppress CTLA-4, which causes activation of T cells.
      - ii. Subsequently, activated T cells cause tissue damage inside the
- colon, which destroys mucosal immunity and disrupts the enteric flora and antibody levels.
- iii. Ultimately, this causes inflammation in the GI mucosa and is manifested in diarrhea and immune-mediated colitis.
- (2) Anti-PD-1 drugs: Diarrhea and colitis with PD-L1 agents have a similar presentation as with PD-1 agents.
- (a) PD-1 inhibitor monoclonal antibodies (e.g., nivolumab, pembrolizumab)
    - i. Nivolumab and pembrolizumab are human immunoglobulin G4 monoclonal antibodies that bind to the PD-1 receptor and block its interaction with PD-L1 and PD-L2.
    - ii. Mechanism of action (Chen et al., 2017)
      - Signaling limits effector function on the activated T cells in the periphery.
      - Depletion of regulatory T cells causes inhibition or block of anti-inflammatory mechanisms.
      - Inhibited cytokine production and widespread immune dysregulation result.
    - iii. PD-1 inhibitors can cause colLAGENOUS colitis (Baroudjian et al., 2016).
      - It is characterized by a subepithelial collagen band (more than 10 mcm) with increased intraepithelial lymphocytes.
      - Blocking the PD-1 pathway may trigger mucosal T lymphocytes.
      - It is diagnosed from colonoscopy with pathologic interpretation.
  - (b) PD-L1 inhibitors (e.g., atezolizumab, avelumab, cemiplimab, durvalumab)
    - i. Mechanism of action: Blockade of the PD-L1 pathway causes an increase in T-cell activation, which ultimately leads to decreased tumor size.
    - ii. When the PD-L1 pathway is blocked, immune responses

are inhibited without causing antibody-dependent cellular cytotoxicity.

iii. Combining checkpoint inhibitors, such as ipilimumab and nivolumab, further increases risk and toxicity (Kroschinsky et al., 2017).

iv. Combination checkpoint inhibitors and radiation therapy to the abdomen also increase toxicity risk, most frequently diarrhea and colitis.

(3) PI3K inhibitors (e.g., idelalisib): mechanism of action

(a) Inhibits PI3K pathway to induce apoptosis of malignant B cells

(b) Causes tissue damage in the colon and mucosal lining, which manifests as diarrhea and immune-mediated colitis (Louie et al., 2015)

## 2. Incidence

a) Neutropenic enterocolitis: True incidence is unknown but is estimated to be approximately 5%–6% of hospitalized adults with hematologic malignancies undergoing chemotherapy or with aplastic anemia. It is frequently underreported (Rodrigues et al., 2017).

b) *C. difficile* colitis

(1) *C. difficile*–associated diarrhea is the most common cause of nosocomial diarrhea in the United States, occurring in upwards of 25% of patients.

(2) Patients with cancer are at a high risk of developing *C. difficile*–associated diarrhea. Of those receiving myelosuppressive cancer therapies, approximately 7% will develop *C. difficile*–associated diarrhea, and of those cases, approximately 8% will develop more severe colitis.

(3) Incidence of positive *C. difficile* blood cultures is 18%–44% (Nesher & Rolston, 2012).

(4) Relapse can occur in as many as 35% of patients (Neemann & Freifeld, 2017).

c) Immune-mediated colitis: Highest rates of GI adverse events occur in patients receiving combination ipilimumab and nivolumab, with all-grade colitis, severe colitis, and severe diarrhea reported in 13.5%, 9.4%, and 9.2%, respectively. Symptoms of diarrhea and colitis generally develop within six to eight weeks of immune checkpoint inhibitor therapy (Thompson et al., 2019).

(1) CTLA-4 monoclonal antibodies

(a) Approximately 40% of patients will experience some form of GI symptomatology, and anywhere from 8% to 22% develop colitis (Dougan et al., 2020; Gupta et al., 2015; Haanen et al., 2017).

(b) Colon perforation occurs in up to 1.5% of patients (Haanen et al., 2017).

(c) The median onset of ipilimumab-induced colitis was 34 days or following three treatments (Cramer & Bresalier, 2017).

(d) Ipilimumab 3 mg/kg: Approximately 7% of patients experienced diarrhea with up to six stools above baseline, with only 5% of patients experiencing colitis (Bristol-Myers Squibb, 2022).

i. The median onset to grade 2 colitis was 1.4 months.

ii. The median onset to grade 3–5 colitis was 1.7 months.

(2) Anti-PD-1 drugs include monoclonal antibodies directed at both PD-1 (e.g., nivolumab, pembrolizumab) and PD-L1 (e.g., avelumab, atezolizumab, cemiplimab, durvalumab) (Baxi et al., 2018).

(a) Up to 61% of patients experience immune-related adverse events, including GI, dermatologic, and hepatic toxicities (Cramer & Bresalier, 2017; Gupta et al., 2015).

(b) Approximately 19% of patients present with diarrhea (Baxi et al., 2018; Cramer & Bresalier, 2017).

(c) Incidence of colitis is much less frequent in patients receiving anti-PD-1 drugs than anti-CTLA-4 therapy. Less than 1% of patients develop colitis on anti-PD-1 therapy (Haanen et al., 2017).

(3) PI3K inhibitors

(a) Idelalisib (Esposito et al., 2019)

(b) Copanlisib (Bayer HealthCare Pharmaceuticals, 2021a; Curigliano & Shah, 2019)

## 3. Risk factors

a) Patients currently receiving an immunotherapy agent that induces colitis are at risk.

b) History of colitis, whether chemotherapy induced or from previous immunotherapy agents, is a risk factor. Patients who received anti-CTLA-4 therapy and had associated colitis had a higher inci-

- dence of colitis when exposed to other immunotherapy agents, such as PD-1 inhibitors (Chen et al., 2017).
- c) Preexisting bowel abnormalities are a risk factor, such as autoimmune diseases (e.g., Crohn disease ulcerative colitis), diverticulitis, history of bowel surgery, and extensive tumor infiltration (Donia et al., 2017).
  - d) Neutropenic enterocolitis can occur in patients receiving high-dose chemotherapy and chemotherapy given for acute leukemia treatment (Palmore et al., 2019).
  - e) Neutropenia is a risk factor, as it reduces the body's immune response and allows for overgrowth of the intestinal microbes (Nesher & Rolston, 2012).
  - f) Radiation therapy increases the risk of mucosal damage and causes injury and destruction to the normal mucosa (Nesher & Rolston, 2012).
  - g) Nonsteroidal anti-inflammatory drug use is associated with an increased risk of anti-CTLA-4-induced colitis (Haanen et al., 2017).
  - h) Antibiotic use is associated with increased risk for the development of *C. difficile*-associated diarrhea and colitis.
  - i) Prior and prolonged hospitalizations for colitis are also risk factors (Neemann & Freifeld, 2017).
4. Clinical manifestations (see Table 15-6)
- a) Neutropenic enterocolitis (Palmore et al., 2019; Rodrigues et al., 2017)
    - (1) Febrile and neutropenic (absolute neutrophil count less than 500/mm<sup>3</sup>)
    - (2) Bowel wall thickening of greater than 4 mm
    - (3) Right lower quadrant inflammatory mass and mucosal edema: Extensive involvement of the large bowel and terminal ileum may occur.
    - (4) Abdominal pain, cramping, and tenderness
    - (5) Nausea, vomiting, and abdominal distension
    - (6) Diarrhea, possibly hematochezia
  - b) Immune-mediated colitis
    - (1) Diarrhea
    - (2) Nausea/vomiting
    - (3) Abdominal pain
    - (4) Possible fever or chills
    - (5) Hematochezia
5. Assessment
- a) History
    - (1) Assess patients for concerning symptoms, including abdominal cramps, nausea/vomiting, oral intake and nutritional status, symptoms of dehydration (e.g., dizziness), fever or chills, changes in mental status, and recent admissions.
  - (2) Assess stool quality and characteristics, including duration, continence, changes in bowel patterns, frequency, consistency, volume, odor, and presence of blood (Fernandes & Andreyev, 2020).
  - (3) Evaluate current or recent medications, including the type of anticancer therapy and any other agents patients are taking or prescribed for symptom management, including herbal remedies and over-the-counter medications.
- b) Physical assessment
- (1) Vital signs
  - (2) Weight
  - (3) Physical examination, with particular attention to the GI system (e.g., visual inspection, palpation, auscultation, presence of guarding or rebound tenderness, assessment for fecal impaction)
  - (4) Signs of dehydration, including decreased skin turgor, decreased urine output, hypotension, tachycardia, and delayed capillary refill
- c) Laboratory assessment
- (1) Stool testing
    - (a) Infectious etiologies: As the oncology patient population is at increased risk for infection, it is important to rule out *C. difficile*, cytomegalovirus via DNA polymerase chain reaction (PCR), ova, and parasites (Brahmer et al., 2018).
    - (b) Inflammatory markers: Fecal calprotectin and lactoferrin are highly sensitive to colonic inflammation. Fecal calprotectin is a stool inflammatory marker that has been widely used in clinical practice for patients with inflammatory bowel disease and is used as a predictive tool for immune-related colitis (Dougan et al., 2020; Tian et al., 2018).
    - (c) Fecal occult blood test
    - (d) Fecal leukocytes
  - (2) Serum chemistries for electrolyte imbalances
  - (3) Albumin
  - (4) Acid-base balance and lactate if sepsis suspected
  - (5) Blood cultures
  - (6) Urinalysis
  - (7) Complete blood count to determine neutropenia, anemia

**TABLE 15-6.** Comparison of Chemotherapy-Induced and Immune-Mediated Colitis

| Characteristic                   | Chemotherapy Induced                                                                                                                                                                                                                                                                                                                                                                                                | Immune Mediated                                                                                                                                                                       |
|----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Distribution                     | Superficial                                                                                                                                                                                                                                                                                                                                                                                                         | Continuous, superficial                                                                                                                                                               |
| Primary location of inflammation | Diffuse pancolitis                                                                                                                                                                                                                                                                                                                                                                                                  | Left colon<br>Distal colon and rectum<br>Diffuse pancolitis                                                                                                                           |
| Suspected etiology               | Predisposition due to neutropenia<br><i>Clostridium difficile</i> and associated toxin<br>Fungal etiologies<br>Cytomegalovirus                                                                                                                                                                                                                                                                                      | CTLA-4 (cytotoxic T-lymphocyte antigen 4), PD-1 (programmed cell death protein 1), or PI3K (phosphoinositide 3-kinase) inhibition<br>T-cell activation<br>Regulatory T-cell depletion |
| Histologic findings              | Bowel wall thickening > 4 mm<br>Various degrees of hemorrhage, ulcerations, and ecchymosis<br>Exudates with fibrin and cellular debris on severely ulcerated areas<br>Microscopic findings: mucosal and submucosal edema with associated necrosis                                                                                                                                                                   | Cryptitis and granulomas<br>Lymphoplasmacytic expansion of lamina propria<br>Apoptotic bodies<br>Neutropenia                                                                          |
| Management                       | Drug hold or discontinuation<br>Bowel rest<br>Antidiarrheal contraindicated<br>Testing to rule out microbial source<br>Consideration of granulocyte-colony-stimulating factor until resolution or absolute neutrophil count > 1,000/mm <sup>3</sup><br>Initiation of empiric antimicrobials<br>Supportive care: fluids/electrolyte replacement; maintaining hemoglobin > 7 g/dl, platelets > 50,000/mm <sup>3</sup> | Drug hold or discontinuation<br>Corticosteroids<br>Use of infliximab in corticosteroid-resistant colitis<br>Surgical intervention as last resort                                      |

Note. Based on information from Anand & Glatt, 1993; Barina et al., 2016; Baroudjian et al., 2016; Bavi et al., 2017; Cramer & Bresalier, 2017; Gupta et al., 2015; Nesher & Rolston, 2012; Palmore et al., 2019; Rodrigues et al., 2017; Weidner et al., 2015; Yanai et al., 2017.

(8) Erythrocyte sedimentation rate and C-reactive protein are used to help diagnose inflammatory disease (Assasi et al., 2015).

(9) HIV, hepatitis A and B, and blood quantiferon testing for tuberculosis should be routinely performed in patients at high risk for those infections in preparation for starting infliximab (Brahmer et al., 2018).

d) Radiographic assessment

(1) CT scan can evaluate bowel perforation, obstruction, toxic megacolon, and intestinal wall thickening. CT scan is 85.2% sensitive and 75% specific for colitis (Dougan et al., 2020).

(2) Another method to detect bowel abnormalities is via a fluorodeoxyglucose positron-emission tomography (FDG-PET)/CT study.

(3) Colonoscopy with biopsies for histologic examination is not recommended if neu-

tropenic enterocolitis is suspected (Puzanov et al., 2017; Rodrigues et al., 2017).

(4) Endoscopic biopsies are the gold standard for diagnosing GI immune-related adverse events from checkpoint inhibitors. The degree of mucosal injury found on endoscopy is the most predictive factor of treatment responsiveness, as opposed to Common Terminology Criteria for Adverse Events grade or severity of symptoms (Dougan et al., 2020; Tian et al., 2018).

(5) Ultrasonography may be used to measure the thickness of the bowel wall and may help measure the clinical course of colitis (Nesher & Rolston, 2012).

e) Differential diagnoses

(1) As neutropenic enterocolitis generally involves pain in the right lower abdominal quadrant, it can mimic acute appendicitis. Other differential diagnoses include *C. difficile* colitis, graft-versus-host dis-



- ease, cytomegalovirus, norovirus, ischemic colitis, and inflammatory bowel disease (Rodrigues et al., 2017).
- (2) *C. difficile* colitis can include other infectious diarrhea, noninfectious complicated diarrhea, inflammatory bowel disease, celiac disease, and immune-mediated colitis (Polage et al., 2012).
  - (3) Neutropenic colitis can include cytomegalovirus infection, opportunistic viral infections, and fungal colitis (Dougan et al., 2020).
6. Collaborative management and prevention
- a) Preventing diarrhea includes early recognition of symptoms.
    - (1) Proper grading of diarrhea is essential for proper management.
    - (2) NCI CTEP's (2017) grading criteria are used to assess symptoms of diarrhea or colitis and implement a treatment management strategy (see Figure 15-8).
  - b) Interprofessional collaboration promotes improved patient outcomes (Mistry et al., 2017).
    - (1) Educate and inform clinicians on identifying, grading, and managing diarrhea and colitis.
    - (2) Early intervention can improve patient outcomes.
    - (3) Minimize the likelihood of permanent or severe side effects.
  - c) Rule out infectious colitis.
    - (1) Perform stool tests for enteric pathogens and *C. difficile* (by PCR) (Gupta et al., 2015).
    - (2) Rule out cytomegalovirus infection by performing immunohistochemical staining on biopsy samples from colonoscopy (Gupta et al., 2015).
    - (3) Rule out fungal causes of colitis.
  - d) Perform diagnostics.
    - (1) Colonoscopy in any patient with grade 2 or higher diarrhea (Cramer & Bresalier, 2017) with biopsies (Puzanov et al., 2017)

**FIGURE 15-8.** Common Terminology Criteria for Adverse Events Grading for Colitis

| Adverse Event | Grade                                                                              |                                         |                                         |                                                              |       |
|---------------|------------------------------------------------------------------------------------|-----------------------------------------|-----------------------------------------|--------------------------------------------------------------|-------|
|               | 1                                                                                  | 2                                       | 3                                       | 4                                                            | 5     |
| Colitis       | Asymptomatic; clinical or diagnostic observations only; intervention not indicated | Abdominal pain; mucus or blood in stool | Severe abdominal pain; peritoneal signs | Life-threatening consequences; urgent intervention indicated | Death |

| Management by Treatment Type |                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |   |   |
|------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|---|
| Immune-mediated colitis      | Grade                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |   |   |
|                              | 1                                                                                                                                                                                                                                                | 2                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 4 | 5 |
|                              | <ul style="list-style-type: none"> <li>Consider holding immunotherapy per National Comprehensive Cancer Network guidelines.</li> <li>Initiate loperamide, oral hydration, and close monitoring.</li> <li>Consider diet modifications.</li> </ul> | <ul style="list-style-type: none"> <li>Hold immunotherapy.</li> <li>Administer IV methylprednisolone (1 mg/kg daily).</li> <li>If no response in 2–3 days:               <ul style="list-style-type: none"> <li>– Increase dose to 2 mg/kg daily.</li> <li>– Consider infliximab.</li> <li>– If refractory to infliximab, consider vedolizumab.</li> </ul> </li> <li>Continue antidiarrheals.</li> <li>Consider gastroenterology consult.</li> </ul> | <ul style="list-style-type: none"> <li>Discontinue anti-cytotoxic T-lymphocyte antigen 4 agents.</li> <li>Anti-programmed cell death protein 1/programmed cell death-ligand 1 therapy may be reinstated after toxicity resolution.</li> <li>Hospitalization may be required for supportive care.</li> <li>Administer IV methylprednisolone (2 mg/kg daily).</li> <li>If no response in 2 days:               <ul style="list-style-type: none"> <li>– Consider infliximab (5–10 mg/kg).</li> <li>– If refractory to infliximab, consider vedolizumab.</li> </ul> </li> </ul> |   | – |

Note. Grading criteria from *Common Terminology Criteria for Adverse Events* [v.5.0], by National Cancer Institute Cancer Therapy Evaluation Program, 2017 ([https://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/docs/CTCAE\\_v5\\_Quick\\_Reference\\_5x7.pdf](https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf)). In the public domain.



- (2) Plain x-rays to visualize dilation of small bowel and gas
- (3) CT scan to visualize bowel wall thickening
- (4) Fecal occult blood test
- (5) Testing to rule out infectious etiologies, including stool and blood cultures and PCR assay for *C. difficile*
- e) Neutropenic enterocolitis
  - (1) Holding chemotherapy
  - (2) Bowel rest (Palmore et al., 2019)
  - (3) Aggressive IV fluid resuscitation (Palmore et al., 2019; Rodrigues et al., 2017)
  - (4) Initiation of broad-spectrum antibiotics with consideration of antifungal agents (Palmore et al., 2019; Rodrigues et al., 2017)
  - (5) Consideration of granulocyte-colony-stimulating factor until resolution or an absolute neutrophil count greater than  $1,000/\text{mm}^3$  (Nesher & Rolston, 2012)
  - (6) Testing to rule out infectious etiologies: Collect stool cultures for fungal sources or cytomegalovirus and perform a PCR assay for *C. difficile* (Rodrigues et al., 2017).
  - (7) Delay of chemotherapy until full resolution and consideration of dose modification for subsequent cycles (Nesher & Rolston, 2012)
  - (8) Surgical intervention may be necessary with perforation, uncontrolled sepsis or GI bleeding, or the development of other conditions, such as abscess (Palmore et al., 2019; Rodrigues et al., 2017).
- f) *C. difficile* colitis
  - (1) *C. difficile* colitis is managed with oral vancomycin or fidaxomicin. Metronidazole is reserved for nonsevere cases for which other treatments may not be available (Palmore et al., 2019).
  - (2) Antidiarrheals are contraindicated because they decrease motility, allowing *C. difficile* bacteria and toxins to fester and overgrow (Anand & Glatt, 1993).
- g) Immune-mediated colitis (see Figure 15-8)
  - (1) Effective colitis and diarrhea management is accomplished by early intervention regardless of the immunotherapy agent.
  - (2) Colitis-related mortality with immunotherapy agents has been associated with delayed reporting, nonadherence with the antidiarrheal regimen, and failure to hold the immunotherapy agent (Naidoo et al., 2015).
  - (3) Early identification and diagnosis with timely implementation of therapy are critical (Gondal et al., 2016).
- (4) With early intervention, colitis is reversible.
- (5) Interventions by grade
  - (a) Grade 1 bowel symptoms: Patients generally respond well to conservative management (Tian et al., 2018).
    - i. Treat symptomatically using antidiarrheals, such as loperamide or diphenoxylate-atropine (Dougan et al., 2020).
    - ii. Monitor for dehydration and institute fluid and electrolyte replacement if needed (Thompson et al., 2019).
    - iii. Consider holding immunotherapy; it may be resumed if toxicity does not worsen or improves (Brahmer et al., 2018).
    - iv. Monitor closely (Thompson et al., 2019).
    - v. Dietary modification should include bland foods; add bulking agents, such as psyllium (Dougan et al., 2020; Puzanov et al., 2017).
  - (b) Grade 2 bowel symptoms
    - i. Hold checkpoint inhibitor therapy and continue treatment with antidiarrheal. Consider permanent discontinuation of CTLA-4 agents; anti-PD-1 agents may be restarted if patients recover to grade 1 or less (Cramer & Bresalier, 2017; Puzanov et al., 2017; Thompson et al., 2019).
    - ii. High-dose corticosteroids should be initiated if suspected colitis or uncomplicated diarrhea does not improve with conservative measures for two to three days (Puzanov et al., 2017). Most patients will respond to first-line treatment with steroids and achieve remission after a four-to-six-week taper. Initiate at 1 mg/kg daily of prednisone or methylprednisolone. If there is no improvement after two to three days, increase to 2 mg/kg daily and consider adding infliximab or vedolizumab (Dougan et al., 2020;

- Puzanov et al., 2017; Thompson et al., 2019). Once symptoms decrease to grade 1 or less, resume therapy, and continue a four-to-six-week steroid taper. Rapid tapering of steroids may result in recurrent colitis (Brahmer et al., 2018; Cramer & Bresalier, 2017).
- iii. Approximately 30%–40% of patients treated with high-dose corticosteroids require secondary immune suppression with a biologic agent. In patients with corticosteroid-resistant colitis, infliximab or vedolizumab, which are monoclonal antibodies that target inflammatory cytokine tumor necrosis factor- $\alpha$ , are recommended. A response is generally seen in one to three infusions (Dogan et al., 2020; Gupta et al., 2015; Yanai et al., 2017).
    - Approximately 17% of patients with ipilimumab-related colitis are treated with infliximab after corticosteroid failure of symptom reduction (Barina et al., 2016).
    - Infliximab is contraindicated in patients with perforation or sepsis (Yang et al., 2017).
    - Early initiation is associated with faster symptom resolution, decreased hospitalization, and decreased recurrence of colitis (Abu-Sbeih et al., 2019; Dogan et al., 2020).
  - iv. Consider gastroenterology consult.
  - v. Loperamide may be continued if infectious etiology is ruled out.
- (c) Grade 3–4 bowel symptoms
- i. Consider permanently discontinuing checkpoint inhibitor therapy and initiating corticosteroids (Puzanov et al., 2017; Thompson et al., 2019).
  - ii. Initiate at 1–2 mg/kg daily of prednisone or equivalent, followed by a one-month steroid taper (Puzanov et al., 2017; Thompson et al., 2019).
  - iii. If grade 3–4 symptoms persist with corticosteroids after three to five days, initiate infliximab or vedolizumab (Puzanov et al., 2017; Thompson et al., 2019).
  - iv. Consider hospitalization with a gastroenterology consult (Brahmer et al., 2018; Dogan et al., 2020).
  - v. Perform an endoscopy to rule out other etiologies of inflammation, including infection, ischemia, new-onset celiac disease, pancreatic insufficiency, and medication-induced diarrhea; assess or reassess mucosal severity (Dogan et al., 2020).
- h) Total colectomy
- (1) Colectomy was used as a definitive treatment in 8% of patients with ipilimumab-related colitis after failure of medical therapy (Barina et al., 2016).
  - (2) Surgery is reserved for patients in whom medical therapy has failed or those with bowel perforation (Gupta et al., 2015).
- i) Management of PD-1 inhibitor-induced colitis (Baroudjian et al., 2016)
- (1) Pembrolizumab-induced collagenous colitis
    - (a) It is recommended to perform a colonoscopy with biopsies.
    - (b) If a diagnosis of collagenous colitis is made with pathology, it is recommended to continue with PD-1 inhibitor therapy while initiating corticosteroid therapy, such as budesonide 9 mg daily, along with symptomatic management.
  - (2) General early intervention includes the withdrawal of PD-1 inhibitor therapy and initiation of steroids.
7. Patient and family education
- a) Educate patients and caregivers on the definition of diarrhea and the importance of reporting bowel movements.
    - (1) Underreporting of diarrheal episodes may cause a delay in therapy.
    - (2) Patients should report to the treatment team any changes in bowel patterns, increase in stools over baseline, fever, abdominal distention, pain or cramping,

nausea, blood in stool, and increased gas (Brahmer et al., 2018).

- b) Although the median onset of colitis and diarrhea has been outlined previously, symptoms of colitis or diarrhea can occur any time after patients have received an immunotherapy or chemotherapy agent.

- (1) Drink fluids to maintain clear or pale yellow-colored urine.
- (2) Eat a well-balanced diet. Patients with mild grade 1 diarrhea or colitis can follow the diet provided by the Academy of Nutrition and Dietetics (Naidoo et al., 2015).
- (3) Work with a dietitian to determine foods that cause flares and avoid those foods.

## E. Pancreatitis

### 1. Overview

- a) Pancreatitis is inflammation of the pancreas classified as either acute or chronic.
- b) Classifications (Greenberg et al., 2016)
  - (1) Acute pancreatitis is mild acute, moderately severe, or severe.
    - (a) Mild acute: absence of organ failure or local or systemic complication
    - (b) Moderately severe: transient organ failure (resolves within 48 hours) or local or systemic complications without persistent organ failure (greater than 48 hours)
    - (c) Severe: persistent organ failure that may involve one or multiple organs
  - (2) Chronic pancreatitis is inflammation of the pancreas that does not heal, worsens over time, and leads to permanent damage (Gardner et al., 2020).

### 2. Guidelines for diagnosis

- a) Acute pancreatitis is the presence of at least two of the following three features: upper abdominal pain, serum amylase or lipase more than three times the upper limit of normal, or imaging suggestive of pancreatitis, such as CT scan, magnetic resonance imaging, or ultrasonography (Greenberg et al., 2016).
- b) Severe pancreatitis is persistent organ failure for more than 48 hours despite IV fluid resuscitation and a serum C-reactive protein level of 150 mg/dl or greater at baseline or in the first 72 hours (Greenberg et al., 2016).
- c) Chronic pancreatitis is best diagnosed using abdominal pain, steatorrhea, or a contrast-enhanced CT scan; however, a CT scan may be inconclusive in the early stages. Magnetic resonance imaging, magnetic resonance cholan-

giopancreatography, or endoscopic ultrasonography with or without biopsy may also be used for diagnosis (Barry, 2018).

### 3. Incidence and risk factors

- a) Treatment with L-asparaginase and PEG-asparaginase, older age, and higher cumulative doses of asparaginase (Lieu et al., 2016). The prevalence of asparaginase-associated pancreatitis is 7%–11%, with median onset after two doses (range 1–11 doses) (Stenger, 2019; Zhang et al., 2020).
- b) Other chemotherapy agents (e.g., carboplatin, cisplatin, cytarabine, ifosfamide, paclitaxel, vinorelbine): Onset is variable and may range from hours to one month after administration (Ngo et al., 2015).
- c) Immune checkpoint inhibitors (e.g., ipilimumab, nivolumab, pembrolizumab, atezolizumab): Patients treated with CTLA-4 inhibitors have an increased incidence of pancreatitis when compared to patients treated with PD-1 inhibitors (George et al., 2019).
- d) Targeted therapies (e.g., axitinib, bosutinib, dasatinib, sorafenib, sunitinib, nilotinib, ponatinib, vemurafenib) (Clamon et al., 2017): Pancreatic effects can range from asymptomatic pancreatic enzyme elevation to acute pancreatitis.
  - (1) Frequency of acute pancreatitis in clinical trials is 0%–4.3% (Clamon et al., 2017).
  - (2) Amylase and lipase elevation frequently are reported with TKIs (Clamon et al., 2017).
  - (3) A meta-analysis evaluating pancreatitis with VEGF receptor TKIs (e.g., sunitinib, sorafenib, pazopanib, axitinib, vandetanib, cabozantinib, ponatinib, regorafenib) observed a 1.95-fold increased risk of all-grade pancreatitis; however, the risk of severe (grade 3 or higher) was not significant (Ghatalia et al., 2015).
- e) Obstructions of the duct system (e.g., periampullary neoplasms), cholelithiasis, and congenital alterations in the ductal system (e.g., pancreas divisum)
- f) Hypertriglyceridemia, hypercalcemia
- g) Diabetes
- h) Tumor lysis syndrome
- i) Post-endoscopic retrograde cholangiopancreatography: Pancreatitis is the most common post-procedure complication. The risk is increased with chronic pancreatitis and after inadvertent cannulation of the pancreatic duct (Phillip et al., 2017).
- j) Alcohol abuse
- k) Illicit drug use

- l) Pediatrics: hematopoietic stem cell transplantation (HSCT)
- m) Infection
- 4. Clinical manifestations (Banks et al., 2013)
  - a) Three main manifestations
    - (1) Acute onset of persistent, severe epigastric abdominal pain, which may be right upper quadrant or, rarely, confined to the left side: Approximately 50% radiates to the back. Pain may be partially relieved by sitting up or bending forward.
    - (2) Pancreatic enzyme elevations
      - (a) Serum amylase: Rises within 6–12 hours. The elevation is greater than three times the upper limit of normal and has a sensitivity for diagnosing acute pancreatitis; if uncomplicated, amylase returns to normal after three to five days.
      - (b) Serum lipase: Rises 4–8 hours after onset of symptoms, peaks at 24 hours, and returns to normal within 8–14 days. These elevations occur earlier, last longer than amylase elevations, and are more sensitive in patients with pancreatitis second to alcohol abuse.
      - (c) Trypsinogen activation peptide: Is elevated early and may help detect early acute pancreatitis and predict severity (Dixit et al., 2016)
    - (3) CT scan positive for signs of pancreatic inflammation
  - b) Other clinical findings (Tang, 2021)
    - (1) Fever
    - (2) Tachycardia and hypovolemia
    - (3) Hypoxemia
    - (4) Dyspnea due to diaphragmatic inflammation
    - (5) Nausea and vomiting: incidence of approximately 90%
    - (6) Jaundice, elevated liver function tests
    - (7) Hypoactive bowel sounds, ileus
    - (8) Leukocytosis, elevated hematocrit from hemoconcentration due to extravasation of intravascular fluid into third space
    - (9) Elevated blood urea nitrogen, hypocalcemia, hyperglycemia, hypoglycemia
    - (10) Hemorrhagic pancreatitis: manifested by ecchymotic discoloration around the umbilicus (Cullen sign) or along the flank (Grey Turner sign); suggests possible retroperitoneal bleeding in the setting of pancreatic necrosis
    - (11) Later complications: hemorrhage, sepsis, multisystem organ failure
- 5. Assessment
  - a) Perform a physical examination to find and document the preceding clinical manifestations.
  - b) The epigastrium may be minimally tender to palpation. With severe pancreatitis, patients may have significant tenderness to palpation, abdominal distention, and hypoactive bowel sounds due to ileus from inflammation (Tang, 2021).
- 6. Collaborative management: Treatment and follow-up will depend on the etiology of pancreatitis and its severity (Bade et al., 2019; Working Group IAP/APA Acute Pancreatitis Guidelines, 2013). The primary treatment is holding or discontinuing any agent that may cause the condition.
  - a) Pancreatitis associated with checkpoint inhibitors may require immunosuppression with corticosteroids (Davies, 2016).
  - b) Pancreatitis associated with L-asparaginase tends to respond after the drug is discontinued and aggressive treatment is initiated. It will most likely recur if the drug is used again (Bade et al., 2019; Lieu et al., 2016). Because reduced L-asparaginase exposure is related to a decreased cure rate in acute lymphoblastic leukemia, the drug should not be discontinued unless pancreatitis is diagnosed. L-asparaginase is contraindicated in patients with a history of severe pancreatitis (Bade et al., 2019).
  - c) Insert a nasogastric tube if patients have nausea and vomiting or ileus to rest the gut and pancreas during the acute phase (Bade et al., 2019; Working Group IAP/APA Acute Pancreatitis Guidelines, 2013).
  - d) Use Ringer's lactate for initial fluid resuscitation (Working Group IAP/APA Acute Pancreatitis Guidelines, 2013).
  - e) Implement nutritional support (Working Group IAP/APA Acute Pancreatitis Guidelines, 2013).
    - (1) Restart oral feeding if pancreatitis is mild, abdominal pain decreases, and inflammatory markers improve.
    - (2) Provide enteral tube feeding if pancreatitis is predicted to be severe. Either the nasojejunal or nasogastric route can be used.
    - (3) Parenteral nutrition is a second-line therapy if tube feeding is not tolerated and nutritional support is required.
  - f) Monitor serum lipase, amylase, glucose, electrolytes, and liver function tests. Amylase and lipase are monitored at baseline, two to three days after administration of PEG-asparaginase, and then weekly for at least four weeks after each dose (Bade et al., 2019).
  - g) Treat hyperglycemia as indicated.

- h) Provide effective pain control and monitor for increasing pain, which may indicate progression of pancreatitis.
  - i) Prevention of infectious complications
    - (1) IV antibiotic therapy is not recommended to prevent infectious complications in acute pancreatitis (Crockett et al., 2018; Working Group IAP/APA Acute Pancreatitis Guidelines, 2013). IV antibiotics should be given with suspected infection with necrotizing pancreatitis (Working Group IAP/APA Acute Pancreatitis Guidelines, 2013).
    - (2) Probiotic prophylaxis is not recommended (Working Group IAP/APA Acute Pancreatitis Guidelines, 2013).
    - (3) Selective gut decontamination has shown some benefits, but further studies are needed (Working Group IAP/APA Acute Pancreatitis Guidelines, 2013).
  - j) Monitor vital signs, urine output, blood urea nitrogen concentrations and hematocrit, oxygen saturation, and condition carefully for signs of hypovolemic shock. It is important to use physiologic metrics and goals to guide initial fluid resuscitation to ensure adequate organ perfusion (James & Crockett, 2018).
7. Patient and family education
- a) Instruct patients to use analgesics for pain control.
  - b) Implement oral and nasal care while patients are NPO (nothing by mouth) with a nasogastric tube.
  - c) Ensure that patients understand the importance of adherence to dietary, pharmacologic, and lifestyle recommendations.
  - d) Ensure that patients and significant others can recognize the early symptoms of pancreatitis, such as abdominal pain, especially associated with vomiting, and instruct them to seek medical intervention when these occur.

## F. Mucositis

1. Overview: Mucositis is a potential complication of systemic cytotoxic therapy, EGFR inhibitors, TKIs, and radiation therapy (Harris et al., 2014). Severe mucositis can contribute to hospitalization, the need for narcotic analgesia or total parenteral nutrition, suboptimal delivery of antineoplastic treatment, and morbidity and mortality (Mercadante et al., 2015). Mucositis and stomatitis are often used interchangeably, but they do not reflect identical processes (Peterson et al., 2015).
  - a) Mucositis refers to inflammatory or ulcerative lesions of the oral mucosa or GI tract resulting

from chemotherapy agents or ionizing radiation (Pulito et al., 2020).

- b) Stomatitis refers to an array of symptoms in the oral cavity, including mucosal inflammation, ulcers, chelates or dry lips, and oral pain (Hartl et al., 2017).
  - c) Alimentary tract mucositis refers to mucosal injury across the oral and GI mucosa continuum from the mouth to the anus (Peterson et al., 2015).
2. Pathophysiology
- a) Historically, oral mucositis was attributed to the direct effects of cytotoxic drugs or radiation therapy on the epithelial stem cells. It is now known to be a result of a complex, sequential series of biologic events that culminate in the destruction of epithelial stem cells and interruption of epithelial renewal, which results in erythema and atrophy of the epithelial tissue (Lalla et al., 2014).
  - b) The current biologic model for oral mucositis includes five phases: initiation, upregulation/activation, signaling and amplification, ulceration, and healing (Lalla et al., 2014).
    - (1) Initiation: Radiation and chemotherapy negatively affect the cells and strands of DNA in the basal epithelium and submucosa. Free radicals (reactive oxygen species) also are generated and play an interfering role in the biologic events of the later stages (Lalla et al., 2014).
    - (2) Upregulation/activation: The negative effect on the cells and DNA and the reactive oxygen species activates a cascade of reactions that produce proinflammatory cytokines. These compounds stimulate several pathways, leading to lesions or the death of basal cells by apoptosis (Lalla et al., 2014). Nuclear factor kappa B results in the upregulation of many genes and the release of proinflammatory cytokines, such as tumor necrosis-alpha, IL-1 beta, and IL-6.
    - (3) Signaling and amplification: In addition to causing direct tissue damage, proinflammatory cytokines activate the production of tissue-damaging tumor necrosis factor-alpha, IL-1 beta, IL-6, and other cytokines that alter mucosal tissues. The release of proinflammatory cytokines damages the cells and provides a positive feedback that amplifies the lesions caused directly by the radiation or chemotherapy (Sonis, 2011).
    - (4) Ulceration: Tissue injury in the GI mucosa appears as ulcers that penetrate through



- the epithelium to the submucosa. Bacteria penetrate the submucosa and stimulate macrophage activity, which increases the release of proinflammatory cytokines. Angiogenesis also is stimulated (Sonis, 2011).
- (5) Healing: Signals from extracellular tissues stimulate epithelial proliferation until the mucosa returns to its normal thickness. Neutropenia may prolong the healing process (Sonis, 2011).
3. Incidence of oral mucositis
- a) Prevalence and incidence are inconsistent because of the lack of standardized scoring criteria, tumor location, different treatment regimens, and underreporting (Villa & Sonis, 2015). Incidence varies depending on cancer treatment, dose, and frequency (Fulton, 2018).
- b) Incidence in HSCT recipients is approximately 80% (Eilers et al., 2019). The intensity of the conditioning regimen, transplant type, and TBI can influence incidence and severity (Chaudhry et al., 2016).
- c) Incidence in patients undergoing head and neck radiation therapy is 65%–90% (Sonis, 2011).
- (1) It occurs in almost all patients treated for cancers of the mouth, oropharynx, and nasopharynx, and approximately two-thirds of patients treated for cancers of the hypopharynx or larynx (Moslemi et al., 2016).
- (2) Concomitant chemotherapy and targeted therapy agents increase risk (Villa & Sonis, 2015).
- d) Stomatitis and diarrhea have been reported with targeted therapies.
- (1) The term *stomatitis* has been used for oral lesions secondary to targeted therapy agents to distinguish from mucositis due to conventional chemotherapy and radiation therapy (Shankar et al., 2017).
- (2) Certain mTOR inhibitors have reported rates of 66% (Shankar et al., 2017).
- (3) Lesions secondary to targeted therapy agents are often accompanied by a skin rash (Al-Dasooqi et al., 2013).
4. Risk factors
- a) Development of mucositis depends on treatment- and patient-related factors (Villa & Sonis, 2016).
- b) Treatment-related factors
- (1) Chemotherapy agents (Chaveli-López & Bagán-Sebastián, 2016)
- (a) Antimetabolites
- i. Increased risk with bolus 5-fluorouracil
- ii. Methotrexate for prophylaxis of graft-versus-host disease following HSCT (Solodokin et al., 2020)
- (b) Antitumor antibiotics
- (c) Alkylating agents, including high-dose melphalan
- (d) Plant alkaloids
- (2) Targeted therapies
- (a) mTOR inhibitors (Shankar et al., 2017)
- (b) TKIs (Califano et al., 2015)
- (3) Immunotherapy agents: PD-1/PD-L1 inhibitor therapy may induce or accelerate oral complications by aberrant cell activation, such as what has been seen in graft-versus-host disease or autoimmune conditions (Jackson et al., 2015).
- (4) Patients receiving myeloablative and reduced-intensity conditioning regimens prior to HSCT have a high incidence and severity of oral mucositis (Chaudhry et al., 2016).
- (5) Radiation therapy
- (a) Radiation therapy following surgical resection in patients with head and neck cancer
- (b) Combined chemotherapy and radiation (Eilers et al., 2019)
- (c) TBI or concomitant radiation therapy to the head or neck (Villa & Sonis, 2015)
- (d) Greater incidence when EGFR inhibitor treatment is added to radiation therapy (De Sanctis et al., 2016)
- (6) Drugs or therapies that alter mucous membranes (Wujcik, 2014)
- (a) Oxygen therapy dries out the mucosal lining.
- (b) Anticholinergics decrease salivary flow (Wujcik, 2014).
- (c) Phenytoin causes gingival hyperplasia.
- (d) Steroids can result in fungal overgrowth.
- c) Patient-related risk factors
- (1) Ill-fitting dentures, as they can irritate the mucosa and break integrity (NCI, 2019)
- (2) Poor oral hygiene, periodontal disease: Periodontitis-associated bacteria have been related to the onset and worsening of ulcerative mucositis (NCI, 2019).
- (3) Persistent alcohol or tobacco use
- (a) Alcohol and tobacco irritate the mucosa and disrupt salivary gland function, affecting microcirculation

and possibly delaying healing (Khairnar et al., 2017).

- (b) Chronic alcohol use is associated with mucosal atrophy and hyper-regeneration of the basal layer cells, increasing susceptibility of the mucosa and predisposing patients to malnutrition (De Sanctis et al., 2016).
  - (4) Xerostomia or hyposalivation
  - (5) Dehydration, as it alters mucosal integrity
  - (6) Poor nutritional status
    - (a) Poor nutrition can lead to delayed healing and an increased risk of breakdown (Maria et al., 2017).
    - (b) Unintentional weight loss before therapy can occur (i.e., more than 5% weight loss over one month or more than 10% in the last six months) (De Sanctis et al., 2016).
    - (c) Low body mass index (less than 18.5 kg/m<sup>2</sup>) can lead to delayed healing and increased risk of breakdown in undernourished patients (Maria et al., 2017).
    - (d) Irritating foods (e.g., acidic, spicy) may inflame and traumatize mucosa (Oral Cancer Foundation, n.d.; Wujcik, 2014).
  - (7) Immunosuppression due to comorbidities
  - (8) Neutropenia
  - (9) Hepatic or renal impairment: inadequate metabolism or excretion of drugs
  - (10) Age (Fulton, 2018)
    - (a) Older patients are at higher risk for severe oral mucositis because of age-related decline in kidney function and decreased creatinine clearance rates, which can affect the excretion of chemotherapy and lead to drugs remaining longer in the circulation, causing more damage.
    - (b) Younger patients (20 years and younger) are also at risk for more severe oral mucositis because of increased epithelial mitotic rates and increased EGFR in epithelial tissue (Treister, 2022).
  - (11) Genetic factors may play a significant role. Animal studies have shown that various gene expression-related changes occur after chemotherapy or radiation therapy (Villa & Sonis, 2016).
5. Clinical manifestations
- a) Presentation of oral mucositis depends on the modality (e.g., chemotherapy, targeted therapy,

immunotherapy, radiation therapy, combined therapy), type of drugs administered, dosage or intensity, and schedule of administration (Villa & Sonis, 2016).

- (1) First signs of mucositis usually begin approximately three to four days after the chemotherapy infusion and when patients complain of mucosal irritation (Shankar et al., 2017). Ulcer formation develops, peaks on days 7–14, and resolves about a week after peaking (Villa & Sonis, 2016).
  - (2) HSCT recipients experience mucositis two to five days following the conditioning regimen (McCullough, 2016).
  - (3) Patients receiving radiation to the head and neck complain of oral soreness and develop erythema at the end of the first week of treatment when cumulative doses reach 10 Gray (Gy). By 12–14 days, when cumulative doses reach 30 Gy, multiple ulcerations develop, and as radiation accumulates, ulcerative lesions become more diffuse and painful. These lesions are then present throughout therapy (usually 60–70 Gy). Ulcerations remain at their peak for at least two weeks following completion of treatment. They usually begin to resolve over two to four weeks but can persist for up to eight weeks (Moslemi et al., 2016; Villa & Sonis, 2015).
  - b) Intensity increases with higher doses of cytotoxic drugs. Drugs that are not usually stomatotoxic at standard doses (e.g., cyclophosphamide) can cause cellular damage to the mucosa at high doses (Keefe et al., 2007).
  - c) Signs and symptoms
    - (1) Oral mucosal changes (e.g., erythema, pallor, white patches, discolored lesion, ulcers), edematous oral mucosa, tongue
    - (2) Mucosal ulcerations: irregularly shaped lesions that typically lack peripheral erythema (Shankar et al., 2017)
    - (3) Mouth lesions with mTOR inhibitors: clinically mimic aphthous stomatitis (commonly called canker sores) (Shankar et al., 2017)
    - (4) Difficulty talking, changes in voice strength, pain when talking
    - (5) Pain on swallowing, inability to swallow
    - (6) Saliva: changes in amount or consistency, watery or thick and ropy
6. Assessment
- a) Use a standardized assessment tool or scale when performing a physical examination. Scales designed for clinical use consider the symp-



toms, signs, and functional disturbances associated with oral mucositis and assign an overall score.

- (1) Oral Assessment Guide: This tool contains eight categories that reflect oral health and function: voice, swallowing, lips, tongue, saliva, mucous membrane, gingiva, and teeth/dentures (Aoki et al., 2019). It has been identified as the only validated tool consistently judged to be user-friendly and appropriate for children and adults (Whithorn, 2021).
- (2) The World Health Organization (1979) Oral Toxicity Scale combines mucosal changes, pain, and functionality into a single composite score (Epstein et al., 2012).
  - (a) Grade 0: no changes
  - (b) Grade 1: soreness, erythema
  - (c) Grade 2: soreness, erythema, ulceration, and can eat solid food
  - (d) Grade 3: soreness, erythema, ulceration, and can consume a liquid diet only
  - (e) Grade 4: soreness, erythema, ulceration, and oral alimentation is not possible
- (3) The World Health Organization tool grades the severity of mucositis, whereas the Oral Assessment Guide addresses overall changes in the oral cavity (Whithorn, 2021).
- (4) NCI CTEP's (2017) *Common Terminology Criteria for Adverse Events* consists of a 1–5 grading scale associated with descriptions of oral mucosal changes.
  - (a) Grade 1: asymptomatic or mild symptoms; intervention not indicated
  - (b) Grade 2: moderate pain or ulcer that does not interfere with oral intake; modified diet indicated
  - (c) Grade 3: severe pain; interfering with oral intake
  - (d) Grade 4: life-threatening consequences; urgent intervention indicated
  - (e) Grade 5: death
- (5) Patient-reported outcome measures are questionnaires completed by patients to assess symptom burden and functionality (Kingsley & Patel, 2017). They allow for clinical interventions to be measured from the patient's perspective of the level of impairment and quality of life (Kingsley & Patel, 2017).

(a) Patient-Reported Oral Mucositis Symptom scale (Kushner et al., 2008; see Figure 15-9).

(b) Oral Mucositis Weekly Questionnaire (Epstein et al., 2007)

(c) Oropharyngeal Mucositis-specific Quality of Life Instrument

b) Whichever tool is used, it should be standard practice for all relevant patients in the health service (Whithorn, 2021).

## 7. Collaborative management and prevention

a) Several different agents and interventions have been studied to prevent and treat mucositis (Shankar et al., 2017). The Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology provide evidence-based guidelines endorsed by the American Society of Clinical Oncology, European Society for Medical Oncology, and Oncology Nursing Society. The Oncology Nursing Society Putting Evidence Into Practice resources provide evidence-based interventions for patient care (Eilers et al., 2019).

b) Good oral hygiene practices and oral care protocols are beneficial and may reduce the risk, duration, and severity of oral mucositis (Shankar et al., 2017).

(1) The most important aspect of any oral care protocol is the consistency of use; oral care positively affects mucositis prevention and management (Eilers et al., 2019).

(2) The protocol should include brushing with a soft toothbrush and flossing at least twice daily (Eilers et al., 2019).

(3) Microorganism colonization of oral ulcerations may prolong healing, so it is important to reduce the oral bacterial load with routine oral hygiene (Shankar et al., 2017).

c) Orthodontic appliances or poorly fitting dentures may traumatize the oral mucosa and should be removed or adjusted (Villa & Sonis, 2016). Braces may need to be removed if patients undergo transplantation or if prolonged periods of neutropenia are anticipated.

d) Patient education may improve adherence with oral care, frequency, and ability to cope with mucositis (Shankar et al., 2017).

e) Conduct a pretreatment dental evaluation with attention to potentially irritating teeth surfaces, underlying gingivitis, periodontal infection, and ill-fitting dentures. Crucial dental work should be done before chemotherapy begins.

f) Emphasize intake of high-protein foods and increased fluid intake (greater than 1,500 ml daily).

**FIGURE 15-9.** Patient-Reported Oral Mucositis Symptom (PROMS) Scale

This questionnaire asks you to evaluate some situations you may have experienced in the past week. All of the situations refer to the condition of your mouth. You can indicate the severity of the situation by placing a vertical mark along the lines below.

**Mouth pain**

No pain \_\_\_\_\_ worst possible pain

**Difficulty speaking because of mouth sores**

No trouble speaking \_\_\_\_\_ impossible to speak

**Restriction of speech because of mouth sores**

No restriction of speech \_\_\_\_\_ complete restriction of speech

**Difficulty eating hard foods (hard bread, potato chips, etc.) because of mouth sores**

No trouble eating hard foods \_\_\_\_\_ impossible to eat hard foods

**Difficulty eating soft foods (Jello, pudding, etc.) because of mouth sores**

No trouble eating soft foods \_\_\_\_\_ impossible to eat soft foods

**Restriction of eating because of mouth sores**

No restriction of eating \_\_\_\_\_ complete restriction of eating

**Difficulty drinking because of mouth sores**

No trouble drinking \_\_\_\_\_ impossible to drink

**Restriction of drinking because of mouth sores**

No restriction of drinking \_\_\_\_\_ complete restriction of drinking

**Difficulty swallowing because of mouth sores**

Not difficult to swallow \_\_\_\_\_ impossible to swallow

**Change in taste**

No change in taste \_\_\_\_\_ complete change in taste

Note. Figure courtesy of Howard C. Tenenbaum, DDS, Dipl Perio, PhD, FRCD(C). Used with permission.

## g) Prevention of oral mucositis

- (1) Oral cryotherapy is recommended for patients receiving bolus 5-fluorouracil or high-dose melphalan with or without TBI, a conditioning regimen for HSCT (Correa et al., 2020). It is important to note that although not for oral mucositis, oral cryotherapy during oxaliplatin infusion has been shown to prevent oral thermal hyperalgesia (oral temperature sensitivity) (Bauman et al., 2019).
- (2) Recombinant human keratinocyte growth factor-1 (palifermin) at a dose of 60 mcg/

kg daily for three days prior to a conditioning treatment and for three days after treatment is recommended in patients receiving high-dose chemotherapy and TBI, followed by autologous HSCT for a hematologic malignancy (Lalla et al., 2014).

- (3) Low-level laser therapy is recommended for patients receiving HSCT conditioned with high-dose chemotherapy with or without TBI and patients receiving radiation therapy without concomitant chemotherapy for head and neck cancer (Lalla et al., 2014).

- (4) Benzydamine mouthwash is recommended for patients with head and neck cancer receiving moderate-dose radiation therapy (up to 50 Gy) without concomitant chemotherapy (Elad et al., 2020).
- (5) Zinc supplements may not help prevent mucositis in patients with oral cancer receiving radiation or chemoradiation (Shuai et al., 2019).
- (6) *Lactobacillus* lozenges have been proven effective in patients with head and neck cancer undergoing chemoradiation (Shankar et al., 2017; Sharma et al., 2012).

#### h) Prevention of GI mucositis

- (1) Amifostine greater than 340 mg/m<sup>2</sup> IV is recommended to prevent proctitis in patients receiving radiation therapy (King et al., 2020).
- (2) If loperamide is ineffective for treating diarrhea induced by standard or high-dose chemotherapy associated with HSCT, octreotide at a dose greater than 100 mcg given subcutaneously twice daily is recommended (Krishnamurthi & Macaron, 2021).
- (3) The following recommendations have been suggested; however, the evidence is weaker:
  - (a) Amifostine IV can prevent esophagitis induced by chemoradiation in patients with non-small cell lung cancer (Elad et al., 2020; King et al., 2020; Lalla et al., 2014). Evidence is available that amifostine lessens the degree and duration of acute mucositis. Still, there are issues to consider, including the frequency of side effects such as nausea and vomiting, difficulty with IV administration, the timing of dose delivery, and the cost of the drug. Any potential benefit should be weighed with the toxicity associated with amifostine (King et al., 2020).
  - (b) Sucralfate enemas can treat chronic radiation-induced proctitis in patients with rectal bleeding who are not neutropenic or thrombocytopenic (Bansal et al., 2016).
  - (c) Sulfasalazine 500 mg twice daily can be used to prevent radiation-induced enteropathy in patients receiving radiation therapy to the pelvis (Pal, 2021).
  - (d) Probiotics containing *Lactobacillus* species are used to prevent diar-

rhea in patients receiving chemotherapy or radiation therapy for a pelvic malignancy (Ciorba et al., 2015).

- (e) Hyperbaric oxygen is used to treat radiation-induced proctitis in patients receiving radiation therapy for a solid tumor (Cooper & Hanley, 2022).

#### i) Symptom control: pain reduction

- (1) Oral agents to promote cleansing, moisture, and comfort (see Table 15-7)
- (2) Patient-controlled analgesia for patients undergoing HSCT
- (3) Use of 2% morphine mouthwash for patients receiving chemoradiation for head and neck cancer (Sarvzadeh et al., 2015)
- (4) Use of 0.5% doxepin mouthwash for all patients with oral mucositis-induced pain (Sio et al., 2019)
- (5) Transdermal fentanyl for patients receiving conventional or high-dose chemotherapy with or without TBI (Shankar et al., 2017)

#### j) Colonization of damaged mucosa by bacteria, fungi, and viruses is thought to occur during the ulceration phase (Vanhoecke et al., 2015). Culture mucosal lesions so that an appropriate antimicrobial agent can be prescribed. *Candida* lesions are white or cream-colored plaques on the mucosa and often are treated while cultures are pending.

#### 8. Patient and family education: Teach oral cavity self-management techniques.

- a) Perform a daily oral self-examination, and report signs and symptoms of mucositis.
- b) Comply with an oral hygiene program. Oral hygiene should be performed after every meal and at bedtime. If mild to moderate dysfunction is present, the frequency of oral hygiene should be increased to every two to four hours. If the condition progresses to more severe dysfunction, hourly care may be indicated. The program should include the following:
  - (1) Floss teeth with dental tape at least once daily or as the clinician advises (Harris et al., 2014).
  - (2) Brush all tooth surfaces with a soft toothbrush for at least 90 seconds at least twice daily. Allow toothbrushes to air dry before storing, and replace toothbrushes frequently (Harris et al., 2014). Sponge swabs are not as effective as toothbrushes and should be avoided when cleaning the teeth, except in patients who cannot tolerate a toothbrush because of severe pain with mucositis. However, sponge swabs may be beneficial for cleaning the mucous

**TABLE 15-7. Mucositis Management**

| Agent                                                                                                        | Efficacy                                                                                                                                                                                                                                                                                                                          | Comments                                                                                                                                                                                                                                                                             |
|--------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Amifostine                                                                                                   | Strong evidence supports the use of amifostine for the prevention of radiation-induced proctitis. Weaker evidence supports use to prevent esophagitis induced by chemoradiation in patients with non-small cell lung cancer.                                                                                                      | Dose of 340 mg/m <sup>2</sup> IV                                                                                                                                                                                                                                                     |
| Benzydamine mouthwash                                                                                        | Strong evidence supports effectiveness in patients with head and neck cancer receiving moderate-dose radiation therapy (up to 50 Gy).                                                                                                                                                                                             | Nonsteroidal anti-inflammatory analgesic<br>Inhibits production of proinflammatory cytokines                                                                                                                                                                                         |
| Chlorhexidine                                                                                                | Chlorhexidine is not recommended for prevention but may have other indications, such as treatment of gingivitis.                                                                                                                                                                                                                  | Contains alcohol<br>Reports of rinse-induced discomfort and taste alteration<br>Can turn teeth brown                                                                                                                                                                                 |
| Cryotherapy (ice chips)                                                                                      | Cryotherapy consistently reduces the incidence and severity of oral mucositis among patients receiving bolus 5-fluorouracil. Weaker evidence supports use for patients receiving high-dose melphalan with or without total body irradiation followed by autologous hematopoietic stem cell transplantation.                       | 30 minutes of cryotherapy suggested prior to 5-fluorouracil therapy<br>Not recommended in patients receiving capecitabine or oxaliplatin because of potential discomfort with exposure to coldness                                                                                   |
| Dexamethasone mouthwash (0.1 mg/ml)                                                                          | Dexamethasone mouthwash is recommended for patients receiving mTOR (mechanistic target of rapamycin) inhibitors.                                                                                                                                                                                                                  | Relieves aphthous-like ulcers, which differ from chemotherapy-induced ulcers, which are irregularly shaped and typically lack peripheral erythema                                                                                                                                    |
| 0.5% doxepin mouthwash                                                                                       | Evidence is weaker but supports the benefit of treating pain.                                                                                                                                                                                                                                                                     | Tricyclic antidepressant with anxiolytic properties                                                                                                                                                                                                                                  |
| Glutamine                                                                                                    | Evidence suggests caution for patients undergoing hematopoietic stem cell transplantation. Oral glutamine is suggested for patients with head and neck cancer receiving chemoradiation.                                                                                                                                           | Essential amino acid                                                                                                                                                                                                                                                                 |
| Honey                                                                                                        | Evidence suggests honey is useful in preventing oral mucositis in patients with head and neck cancer receiving radiation therapy or chemoradiation.                                                                                                                                                                               | Carbohydrate compound                                                                                                                                                                                                                                                                |
| Keratinocyte growth factor-1: palifermin                                                                     | Palifermin is approved to prevent oral mucositis in patients undergoing autologous hematopoietic stem cell transplantation receiving high-dose chemotherapy or total body irradiation.                                                                                                                                            | 60 mcg/kg/day IV for 3 days prior to the preparatory regimen and for 3 days post-transplant<br>Can cause tongue discoloration and an unpleasant aftertaste                                                                                                                           |
| Low-level laser therapy                                                                                      | Low-level laser therapy to reduce incidence of oral mucositis is recommended in patients receiving high-dose chemotherapy with or without total body irradiation before hematopoietic stem cell transplantation and suggested in patients with head and neck cancer receiving radiation therapy without concomitant chemotherapy. | Requires expensive equipment and specialized operator training; limited to centers capable of supporting this technology                                                                                                                                                             |
| Mixed rinses, which may include lidocaine, diphenhydramine, magnesium hydroxide (milk of magnesia), Mylanta® | Data demonstrating efficacy are lacking for the prevention and treatment of mucositis.                                                                                                                                                                                                                                            | Agents potentially useful for pain or discomfort only<br>Alcohol-based elixirs to be avoided<br>May adhere to mucous membranes and build up residue, making oral care difficult or uncomfortable<br>Potential of some preparations to contribute to tooth decay due to sugar content |

(Continued on next page)

**TABLE 15-7. Mucositis Management (Continued)**

| Agent                                    | Efficacy                                                                                                                                         | Comments                                                                                                                                                                                                |
|------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2% morphine mouthwash                    | Evidence is weaker but supports effectiveness.                                                                                                   | For patients receiving chemoradiation for head and neck cancer<br>Limited utility with topical morphine<br>Potential for burning with oral alcohol-based formulations                                   |
| Mucosal coating agents                   | Evidence from randomized trials is lacking to support benefit.                                                                                   | Variety of agents: Gelclair®, Orabase®, sucralfate suspension                                                                                                                                           |
| Nonalcohol-based bland rinses            | Evidence may be insufficient or lacking; however, bland rinses are harmless and can be helpful for oral hygiene maintenance and patient comfort. | 0.9% saline, sodium bicarbonate, or 0.9% saline plus sodium bicarbonate<br>Sodium bicarbonate recommended by Oncology Nursing Society Putting Evidence Into Practice                                    |
| Octreotide                               | Strong evidence supports effectiveness.                                                                                                          | Dose of $\geq 100$ mcg subcutaneously twice daily to treat diarrhea induced by standard- or high-dose chemotherapy associated with hematopoietic stem cell transplantation if loperamide is ineffective |
| Oral zinc supplements                    | Evidence is weaker but supports effectiveness in patients receiving radiation therapy or chemoradiation for head and neck cancer.                | Essential trace element needed for tissue repair; has an antioxidant effect                                                                                                                             |
| Patient-controlled analgesia             | Strong evidence supports its effectiveness in treating pain.                                                                                     | Recommended for patients undergoing hematopoietic stem cell transplantation                                                                                                                             |
| Probiotics: <i>Lactobacillus</i> species | Evidence is weaker but supports effectiveness.                                                                                                   | To prevent diarrhea in patients receiving chemotherapy or radiation therapy for a solid tumor                                                                                                           |
| Sucralfate enemas                        | Weaker evidence supports effectiveness.                                                                                                          | For chronic radiation-induced proctitis in patients with rectal bleeding                                                                                                                                |
| Topical lidocaine                        | Limited data exist; use may provide significant relief of limited duration.                                                                      | Requires frequent application; may lead to decreased sensitivity and additional trauma and impair taste perception<br>Prophylaxis not recommended                                                       |

Note. Based on information from Eilers et al., 2019; Elad et al., 2020; Harris et al., 2014; Lalla et al., 2014; Maria et al., 2017; McGuire et al., 2013; Peterson et al., 2015; Pilotte et al., 2011; Van Seville et al., 2015; Wardill et al., 2014.

membranes of the oral cavity (Harris et al., 2014).

- (3) Cleanse the oral cavity after meals, at bedtime, and at other times by vigorously swishing the mouth with a nonalcohol bland rinse. Oral rinsing should be done to remove excess debris, hydrate the oral mucosa, and aid in removing organisms (Treister, 2022).
- (4) Apply water-based moisturizers to lips.
- (5) Maintain hydration.
- (6) Consider using oral moisturizers to promote comfort if xerostomia exists.
- (7) Avoid irritating agents, including commercial mouthwashes containing phenol, astringents, or alcohol; highly abrasive types of toothpaste; acidic, hot, or spicy

foods and beverages; rough foods; alcohol; tobacco; poorly fitting dentures; braces; and lemon-glycerin swabs and solutions (Harris et al., 2014).

- (8) Recommendations for patients with dentures (NCI, 2019)
  - (a) Remove dentures and other oral devices when cleaning the mouth. If mouth sores are present, or if the mouth is inflamed or painful, avoid using removable oral devices to prevent further irritation.
  - (b) Brush and rinse dentures daily.
  - (c) Clean dentures twice daily with a denture cleaner, and rinse well.
  - (d) Report pain associated with mucositis.

## G. Perirectal cellulitis

1. Overview: Perirectal cellulitis is inflammation and edema of the perineal and rectal area.
2. Pathophysiology
  - a) Tears of the anorectal mucosa allow infection. The most common anaerobic organisms include *Bacteroides fragilis*, *Peptostreptococcus*, *Prevotella*, *Fusobacterium*, *Porphyromonas*, and *Clostridium*. The most common aerobic bacteria include *Staphylococcus aureus*, *Streptococcus*, and *Escherichia coli*. Community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) has been implicated in rectal abscess infections (Hebra, 2020).
  - b) A perianal abscess is a simple anorectal abscess.
  - c) Perirectal abscesses are more complex and involve different planes in the anorectum (Choe et al., 2018).
  - d) Infection starting as a local abscess can lead to systemic sepsis.
3. Incidence: Overall incidence has decreased in the past decade, presumably because of the early use of empiric antibiotics in patients with febrile neutropenia. Perirectal abscesses are more common in patients with anorectal cancer or hematologic malignancies and may be present at the initial diagnosis (Hebra, 2020).
4. Risk factors (Hebra, 2020)
  - a) Chronic neutropenia or thrombocytopenia
  - b) Constipation: The passage of hard stool causes trauma to the rectal mucosa.
  - c) Diarrhea: Caustic fluid irritates and breaks down perirectal tissue.
  - d) Perirectal mucositis caused by chemotherapy or radiation therapy
  - e) Any rectal trauma, such as rectal stimulation or the use of rectal thermometers, enemas, or suppositories
  - f) Hemorrhoids or anal fissures/abscesses
5. Assessment
  - a) Ask patients if they are experiencing perineal or rectal discomfort.
    - (1) Patients with an anorectal abscess often present with severe pain in the anal or rectal area. Pain is constant and not necessarily associated with a bowel movement (Rizzo et al., 2010). Pain may be described as dull, aching, or throbbing, which may worsen when sitting or before defecation.
    - (2) Fear of defecation related to pain may not be reported and may increase the risk of constipation.
  - b) Monitor for the presence of fever.
  - c) Perform a physical examination of the perineal area. The entrance site for the infective agent

may be a small tear that shows minimal irritation.

- (1) An area of fluctuance or patch of erythematous indurated skin overlying perianal skin may be seen with a superficial perianal abscess (Vogel et al., 2016).
  - (2) Localized tenderness, gross swelling, fluctuance, erythema, and drainage may be observed if an abscess is present. An abscess of the perirectal area may produce bloody, purulent, or mucoid drainage.
  - (3) Deeper abscesses may not have findings on physical examination and may only be discovered via digital rectal examination or by imaging (Vogel et al., 2016).
  - (4) If possible, obtain a culture to identify infectious organisms (Hebra, 2020).
- d) Consider an abdominal or pelvic CT scan if an abscess is suspected. Magnetic resonance imaging and transperitoneal or endorectal ultrasound can confirm a diagnosis when a deep abscess is suspected (Vogel et al., 2016).
6. Collaborative management
  - a) Ensure that antibiotic coverage includes a specific anaerobic agent and broad-spectrum aerobic coverage. Consider *Enterococcus* or *Candida* coverage if appropriate (NCCN, 2022b).
  - b) The primary treatment for an anorectal abscess is surgical drainage. Any undrained abscess can expand and progress to systemic infection (Abcarian, 2011).
  - c) Administer antipyretic medications to relieve fever.
  - d) Teach and encourage patients to take sitz baths or use gentle external perineal irrigation (Hebra, 2020).
  - e) Administer stool softeners and encourage patients to eat a low-bulk diet. Consult a dietitian as needed (Hebra, 2020).
  - f) Inspect the perirectal mucosa frequently for any signs of irritation or skin breakdown.
7. Patient and family education
  - a) Instructions for patients and significant others
    - (1) Maintain meticulous perineal hygiene, especially in the presence of neutropenia.
    - (2) Apply appropriate barrier creams.
    - (3) Monitor carefully for any signs of infection or worsening of tissue integrity.
  - b) Ensure that patients and significant others can perform the following:
    - (1) Identify the risk factors for perirectal cellulitis.
    - (2) Implement measures that minimize the risk of developing perirectal cellulitis.



- (3) Identify situations that require prompt, professional intervention.
  - (a) Pain, redness, or swelling in the affected area
  - (b) Body temperature greater than 100.4°F (38°C)

## H. Constipation

1. Overview: Constipation is the slow movement of stool through the intestines characterized by infrequent bowel movements, hard stool, the sensation of abdominal bloating or cramping, straining with bowel movements, and feeling of incomplete evacuation (Davies et al., 2020; Larkin et al., 2018; Rogers et al., 2020).
  - a) It is commonly associated with decreased frequency in defecation of less than three bowel movements in a week and is often accompanied by abdominal discomfort or distention, excessive flatulence, or rectal pressure (Camp-Sorrell, 2018; Larkin et al., 2018).
  - b) If left untreated, constipation can lead to morbidity, including malnutrition, fatigue, hemorrhoids, anal fissures, and in severe cases, GI perforation (Davies et al., 2020; McQuade et al., 2016; Wickham, 2020).
  - c) Constipation may be a presenting symptom of the cancer diagnosis, a side effect of therapy, the result of tumor progression, or unrelated to cancer or its treatment.
  - d) The cause is usually multifactorial; the most common are decreased bowel motility due to decreased fiber intake, dehydration, immobility, and narcotic pain medications (Larkin et al., 2018).
2. Pathophysiology: A decrease in intestinal motility results from one of the following mechanisms (Davies et al., 2020; Larkin et al., 2018).
  - a) Primary or functional: intrinsic factors that slow peristalsis, such as decreased physical activity, lack of time or privacy for defecation, and decreased fiber in the diet
  - b) Secondary: pathologic processes, such as autonomic nervous system dysfunction, preexisting bowel disorders, obstruction, spinal cord compression from tumor, hypercalcemia, hypokalemia, and hypothyroidism
  - c) Iatrogenic: use of pharmacologic agents, such as opioids, chemotherapy, anticonvulsants, and psychotropic medications (Larkin et al., 2018; NCCN, 2022c)
3. Incidence
  - a) Constipation is reported as one of the most common problems for patients with cancer; however, its incidence is not well defined.
  - b) In patients with cancer, the constipation rate is 43%–58%, whereas, in patients with advanced cancer, constipation is reported at 40%–90% (Davies et al., 2020; Larkin et al., 2018; NCCN, 2022c; Rogers et al., 2020).
  - c) Opioid-induced constipation impacts up to 97% of patients with cancer (Davies et al., 2020).
  - d) In 85%–95% of cases, constipation decreases quality of life, even though two-thirds may be mild to moderate (Dzierżanowski & Ciałkowska-Rysz, 2015).
4. Clinical manifestations (Larkin et al., 2018; McQuade et al., 2016; NCI, 2022b)
  - a) Abdominal distention, discomfort, or rectal discomfort or pain
  - b) Nausea and vomiting
  - c) Anorexia
  - d) Impaction and obstruction
  - e) Ileus
  - f) Anal fissures
  - g) Hemorrhoids
  - h) Urinary retention
  - i) Ruptured bowel and life-threatening sepsis
5. Risk factors (Davies et al., 2020; Larkin et al., 2018; NCI, 2022b; Wickham, 2020)
  - a) Disease related: mesenteric and omental masses or malignant adhesions, internal or external obstruction of the bowel by tumor
  - b) Mechanical pressure on the bowel: bowel obstruction second to the tumor in the GI tract, pressure from ascites
  - c) Spinal cord injury or compression
  - d) Bowel disorders: irritable bowel syndrome, Crohn disease
  - e) Neurologic disorders: stroke, Parkinson disease, multiple sclerosis
  - f) Systemic disorders: lupus, amyloidosis, scleroderma
  - g) Decreased mobility
  - h) Anorexia causing poor nutritional intake
  - i) Metabolic and endocrine disorders: hypothyroidism, hyperthyroidism, diabetes mellitus
  - j) Electrolyte disturbances: hypokalemia, hypercalcemia
  - k) Treatment related (see Table 15-8)
    - (1) Neurotoxic effects: cancer chemotherapy, targeted therapy, or immunotherapy agents
    - (2) Surgical: manipulation of intestines, surgical trauma to neurogenic pathways of intestines or rectum
    - (3) Radiation therapy: radiation fibrosis (NCI, 2022b; Wickham, 2020)
    - (4) Nutritional deficiencies: decreased intake of fiber, roughage, and fluids



**TABLE 15-8.** Common Cancer Treatments With High Risk for Constipation

| Causative Agent | Agents                                                                                                    | Mechanism of Action                                                                                                                                                                                                    |
|-----------------|-----------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Antiemetics     | 5-HT <sub>3</sub> receptor antagonists: ondansetron, granisetron, palonosetron, netupitant, palonosetron, | Increases colonic transit time                                                                                                                                                                                         |
| Opioids         | Opioid analgesics: fentanyl, hydrocodone, codeine, hydromorphone, morphine, oxycodone, methadone          | Affects the ability of the small bowel and colon to maintain motility and peristalsis<br>Affects electrolyte and water secretion and absorption in the bowel<br>Primary agents causing medication-induced constipation |
| Radiation       | Radiation to the bowel or abdominal field                                                                 | Fibrosis                                                                                                                                                                                                               |

Based on information from Davies et al., 2020; Larkin et al., 2018; National Comprehensive Cancer Network, 2022b, 2022c; Wickham, 2020.

- (5) Side effects of pharmacologic agents (NCI, 2022b; Wickham, 2020; see Figure 15-10)

- (a) Antineoplastics
- (b) Anticholinergics
- (c) Diuretics
- (d) Opioids
- (e) Aluminum- and calcium-based antacids
- (f) Calcium and iron supplements
- (g) Tricyclic antidepressants
- (h) Antihypertensives
- (i) Antispasmodics
- (j) 5-HT<sub>3</sub> antagonists
- (k) Nonsteroidal anti-inflammatory drugs
- (l) Barbiturates

- (6) Personal factors (Davies et al., 2020; Dzierżanowski & Ciałkowska-Rysz, 2015; NCI, 2022b; Wickham, 2020)

- (a) Interference with usual bowel movement routine
- (b) Lack of privacy
- (c) Lack of response to the defecation reflex: pain, fatigue, social circumstances

- (d) Depression, anxiety
- (e) Decreased physical activity/exercise
- (f) Overuse of laxatives

6. Assessment: Assessment is a key component in preventing and managing opioid-induced and nonopioid-induced constipation. All patients with cancer should be evaluated for constipation and routinely reassessed if constipation is present (Davies et al., 2020; Larkin et al., 2018; Mesía et al., 2019; NCI, 2022b; Wickham, 2020).

- a) Assess the presence of risk factors.
- b) Determine facts about the patient's last bowel movement (e.g., when it occurred, amount, consistency, color, presence of blood). Structured self-rating tools can be useful for a more accurate assessment of constipation. Available tools are the Bristol Stool Form Scale, Constipation Assessment Scale, Common Terminology Criteria for Adverse Events, Patient Assessment of Constipation–Symptoms, bowel function diary, and bowel function index (Larkin et al., 2018; Mesía et al., 2019; NCI CTEP, 2017; Ueberall et al., 2011; Wickham, 2020).
- c) Using the Rome IV Diagnostic Criteria for Opioid-Induced Constipation, assess for new or worsening symptoms when starting and changing opioid therapy. Assess for straining, lumpy or hard stools, a sensation of incomplete evacuation, a sensation of anorectal blockage or obstruction, the need to manually disimpact stool (more than 25% of the time), patient perception of distress related to bowel movement, and less than three bowel movements a week (Gaertner et al., 2015; Rome Foundation, 2016).
- d) Assess usual dietary patterns, focusing on fluid and fiber intake.
- e) Assess mobility, activity level, and functional status.
- f) Assess for abdominal pain, distension, and presence or absence of bowel sounds.
- g) Assess for the presence of straining, rectal pressure, excessive flatulence, or cramping.
- h) Determine current medication usage.
- i) Use laboratory results to assist in the metabolic evaluation.
- j) Perform abdominal palpation and rectal examination if appropriate. A rectal examination is not routinely performed in pediatric patients. Rectal or stoma manipulation for examinations, enemas, or suppositories should be avoided in patients who are myelosuppressed because of the risk of bleeding, fissures, or abscesses (NCI, 2022b; Wickham, 2020).

**FIGURE 15-10.** Oncolytic Agents With Increased Risk of Constipation

| Chemotherapy agents                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>• Alkylating agents               <ul style="list-style-type: none"> <li>– Bendamustine (Bendeka<sup>®</sup>; Teva Pharmaceuticals, 2020a)</li> <li>– Carmustine (BiCNU<sup>®</sup>; Bristol-Myers Squibb, 2007)</li> <li>– Temozolomide (Temodar<sup>®</sup>; Merck, 2019b)</li> <li>– Trabectedin (Yondelis<sup>®</sup>; Janssen Biotech, 2020d)</li> <li>– Vincristine liposomal (Marqibo<sup>®</sup>; Acrotech Biopharma, 2020b)</li> </ul> </li> <li>• Vinca alkaloids               <ul style="list-style-type: none"> <li>– Vinblastine (Velban<sup>®</sup>; Bedford Laboratories, 2012)</li> <li>– Vincristine (Oncovin<sup>®</sup>; Hospira, 2021)</li> <li>– Vinorelbine (Navelbine<sup>®</sup>; GlaxoSmithKline, 2020)</li> </ul> </li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | <ul style="list-style-type: none"> <li>• Immunomodulatory agents               <ul style="list-style-type: none"> <li>– Lenalidomide (Revlimid<sup>®</sup>; Celgene, 2021d)</li> <li>– Pomalidomide (Pomalyst<sup>®</sup>; Celgene, 2021c)</li> <li>– Thalidomide (Thalomid<sup>®</sup>; Celgene, 2021e)</li> </ul> </li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Immunotherapy agents                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <ul style="list-style-type: none"> <li>• Antibody-drug conjugates               <ul style="list-style-type: none"> <li>– Ado-trastuzumab emtansine (Kadcyla<sup>®</sup>; Genentech, 2020b)</li> <li>– Brentuximab vedotin (Adcetris<sup>®</sup>; Seagen, 2020)</li> <li>– Fam-trastuzumab deruxtecan-nxki (Enhertu<sup>®</sup>; Daiichi Sankyo, 2021)</li> <li>– Gemtuzumab ozogamicin (Mylotarg<sup>™</sup>; Wyeth Pharmaceuticals, 2020)</li> <li>– Sacituzumab govitecan-hziy (Trodelvy<sup>™</sup>; Immunomedics, 2020)</li> </ul> </li> <li>• Checkpoint inhibitors: PD-L1 (programmed cell death-ligand 1)               <ul style="list-style-type: none"> <li>– Atezolizumab (Tecentriq<sup>®</sup>; Genentech, 2021f)</li> <li>– Durvalumab (Imfinzi<sup>®</sup>; AstraZeneca Pharmaceuticals, 2020a)</li> </ul> </li> <li>• Monoclonal antibodies               <ul style="list-style-type: none"> <li>– Bevacizumab (Avastin<sup>®</sup>; Genentech, 2021b)</li> <li>– Bevacizumab-awwb (Mvasi<sup>®</sup>; Amgen, 2021b)</li> <li>– Bevacizumab- bvzr (Zirabev<sup>™</sup>; Pfizer, 2021e)</li> <li>– Daratumumab (Darzalex<sup>®</sup>; Janssen Biotech, 2020b)</li> <li>– Elotuzumab (Empliciti<sup>®</sup>; Bristol-Myers Squibb, 2019)</li> <li>– Margetuximab-cmkb (Margenza<sup>™</sup>; MacroGenics, 2020)</li> <li>– Rituximab and hyaluronidase (Rituxan Hycela<sup>®</sup>; Genentech, 2021e))</li> </ul> </li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | <ul style="list-style-type: none"> <li>• Bispecific antibody               <ul style="list-style-type: none"> <li>– Amivantamab-vmjw (Rybrevant<sup>™</sup>; Janssen Biotech, 2021)</li> </ul> </li> <li>• Chimeric antigen receptor T-cell therapy               <ul style="list-style-type: none"> <li>– Axicabtagene ciloleucel (Yescarta<sup>™</sup>; Kite Pharma, 2021b)</li> <li>– Brexucabtagene autoleucel (Tecartus<sup>™</sup>; Kite Pharma, 2021a)</li> <li>– Lisocabtagene maraleucel (Breyanzi<sup>®</sup>; Bristol-Myers Squibb, 2021a)</li> <li>– Tisagenlecleucel (Kymriah<sup>®</sup>; Novartis Pharmaceuticals, 2020c)</li> </ul> </li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Targeted therapies                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <ul style="list-style-type: none"> <li>• ALK (anaplastic lymphoma kinase) inhibitors               <ul style="list-style-type: none"> <li>– Alectinib (Alecensa<sup>®</sup>; Genentech, 2021a)</li> </ul> </li> <li>• BCR-ABL1 (breakpoint cluster-Abelson) inhibitors               <ul style="list-style-type: none"> <li>– Nilotinib (Tasigna<sup>®</sup>; Novartis Pharmaceuticals, 2020d)</li> <li>– Ponatinib (Iclusig<sup>®</sup>; Ariad Pharmaceuticals &amp; Takeda Oncology, 2020)</li> </ul> </li> <li>• CDK (cyclin-dependent kinase) inhibitor               <ul style="list-style-type: none"> <li>– Ribociclib (Kisqali<sup>®</sup>; Novartis Pharmaceuticals, 2020b)</li> </ul> </li> <li>• EZH2 (enhancer of zeste homolog 2) inhibitor               <ul style="list-style-type: none"> <li>– Tazemetostat (Tazverik<sup>®</sup>; Epizyme, 2021)</li> </ul> </li> <li>• FGFR (fibroblast growth factor receptor) inhibitors               <ul style="list-style-type: none"> <li>– Infigratinib (Truseltiq<sup>®</sup>; QED Therapeutics, 2021)</li> <li>– Pemigatinib (Pemazyre<sup>®</sup>; Incyte, 2021)</li> </ul> </li> <li>• HDAC (histone deacetylases) inhibitor               <ul style="list-style-type: none"> <li>– Belinostat (Beleodaq<sup>®</sup>; Acrotech Biopharma, 2020a)</li> </ul> </li> <li>• Hedgehog inhibitors               <ul style="list-style-type: none"> <li>– Glasdegib (Daurismo<sup>®</sup>; Pfizer, 2020b)</li> <li>– Vismodegib (Erivedge<sup>®</sup>; Genentech, 2020a)</li> </ul> </li> <li>• IDH1 (isocitrate dehydrogenase genes) inhibitor               <ul style="list-style-type: none"> <li>– Ivosidenib (Tibsovo<sup>®</sup>; Seattle Genetics, 2021)</li> </ul> </li> <li>• Kinase inhibitors               <ul style="list-style-type: none"> <li>– Axitinib (Inlyta<sup>®</sup>; Pfizer, 2020c)</li> <li>– Cabozantinib (Cometriq<sup>®</sup>, Cabometyx<sup>®</sup>; Exelixis, 2020, 2021)</li> <li>– Crizotinib (Xalkori<sup>®</sup>; Pfizer, 2021d)</li> <li>– Erdafitinib (Balversa<sup>®</sup>; Janssen Biotech, 2020a)</li> </ul> </li> </ul> | <ul style="list-style-type: none"> <li>• KIT (proto-oncogene) inhibitor               <ul style="list-style-type: none"> <li>– Ripretinib (Qinlock<sup>®</sup>; Deciphera Pharmaceuticals, 2021)</li> </ul> </li> <li>• Multikinase inhibitors               <ul style="list-style-type: none"> <li>– Gilteritinib (Xospata<sup>®</sup>; Astellas Pharma, 2019)</li> <li>– Midostaurin (Rydapt<sup>®</sup>; Novartis Pharmaceuticals, 2021c)</li> </ul> </li> <li>• PARP (poly [ADP-ribose] polymerase) inhibitors               <ul style="list-style-type: none"> <li>– Niraparib (Zejula<sup>®</sup>; GlaxoSmithKline, 2021b)</li> <li>– Rucaparib (Rubraca<sup>®</sup>; Clovis Oncology, 2020)</li> </ul> </li> <li>• PDGFR (platelet-derived growth factor receptor) inhibitor               <ul style="list-style-type: none"> <li>– Avapritinib (Ayvakit<sup>™</sup>; Blueprint Medicines, 2021a)</li> </ul> </li> <li>• Proteasome inhibitor               <ul style="list-style-type: none"> <li>– Bortezomib (Velcade<sup>®</sup>; Millennium Pharmaceuticals, 2019)</li> </ul> </li> <li>• RET (rearranged during transfection) inhibitors               <ul style="list-style-type: none"> <li>– Pralsetinib (Gavreto<sup>™</sup>; Blueprint Medicines, 2021b)</li> <li>– Selpercatinib (Retevmo<sup>™</sup>; Eli Lilly and Company, 2021)</li> </ul> </li> <li>• Reversible proteasome inhibitors               <ul style="list-style-type: none"> <li>– Ixazomib (Ninlaro<sup>®</sup>; Millennium Pharmaceuticals, 2021)</li> </ul> </li> <li>• TRK (tropomyosin receptor kinase) inhibitors               <ul style="list-style-type: none"> <li>– Entrectinib (Rozlytrek<sup>®</sup>; Genentech, 2019b)</li> <li>– Larotrectinib (Vitrakvi<sup>®</sup>; Bayer HealthCare Pharmaceuticals, 2021b)</li> </ul> </li> <li>• XPO (exportin 1) inhibitor               <ul style="list-style-type: none"> <li>– Selinexor (Xpovio<sup>®</sup>; Karyopharm Therapeutics, 2021)</li> </ul> </li> </ul> |

- k) Use radiographic imaging to differentiate between mechanical obstruction and decreased motility from an ileus.
7. Collaborative management: The cause of constipation is often multifactorial and should be considered prior to initiating treatment. Management of constipation should be individualized to the patient and based on opioid use and care goals. It should also balance lifestyle modifications and nonpharmacologic approaches with pharmacologic approaches as appropriate (Larkin et al., 2018; Rogers et al., 2020). Although many treatment options exist for constipation, optimal pharmacologic management of constipation in patients with cancer requires further investigation (Davies et al., 2020; Ginex et al., 2020; Larkin et al., 2018; Rogers et al., 2020). The Oncology Nursing Society, Multinational Association of Supportive Care in Cancer, European Society for Medical, and NCCN (2022c) palliative care guidelines offer guidance for treating opioid-induced and nonopioid-induced constipation. Nurses must know the GI side effects of medications and anticipate which patients are at increased risk for constipation. Prevention of constipation is a priority in patients with cancer. Patients on opioids should be considered for a prophylactic bowel regimen with stimulant and osmotic laxatives prior to initiation of opioid therapy (NCCN, 2022c; Rogers et al., 2020).
- a) Pharmacologic interventions (see Table 15-9)
- (1) Peripherally acting mu-opioid receptor antagonists (PAMORAs) are used to treat constipation caused by opioid pain medication. Current PAMORAs include subcutaneous methylnaltrexone, oral methylnaltrexone, and oral naldemedine (Davies et al., 2020).
    - (a) PAMORAs work by protecting the bowel from the effects of the opioid at the receptor sites in the bowel.
    - (b) In patients with laxative-resistant opioid-induced constipation, PAMORAs combined with a bowel regimen should be considered (Davies et al., 2020; Larkin et al., 2018; Rogers et al., 2020).
    - (c) The decision to use PAMORAs should be balanced with the benefit of opioid-constipation relief with potentially undesirable side effects (Rogers et al., 2020).
  - (2) Osmotic laxatives increase the bulk of stools by attracting and retaining water in the bowel, resulting in a softer stool (NCI, 2022b).
    - (a) Lactulose
    - (b) Sorbitol
    - (c) Polyethylene glycol (Miralax®)
  - (3) Stimulant laxatives chemically stimulate the smooth muscles of the bowel to increase contractions (NCI, 2022b).
    - (a) Bisacodyl (Dulcolax®)
    - (b) Senna (Senokot®)
  - (4) Emollient and lubricant laxatives soften hardened feces and facilitate the passage through the lower intestine (NCI, 2022b; Wickham, 2017, 2020).
    - (a) Docusate
    - (b) Mineral oil
    - (c) Glycerin suppository
    - (d) Enema: phosphate (Fleet®), microenema, mineral oil
  - (5) Bulk-forming laxatives increase bowel water absorption, leading to softer stools (NCI, 2022b; Wickham, 2017). They have limited use in cancer-related constipation. These agents are not recommended for patients with advanced cancer or opioid-induced constipation (Larkin et al., 2018; McQuade et al., 2016; Wickham, 2017).
- b) Nonpharmacologic management to prevent constipation
- (1) Include increased physical activity or passive exercise as appropriate (Larkin et al., 2018; NCI, 2022b). This promotes the urge to defecate by helping to move feces into the rectum.
  - (2) Help patients to maintain usual bowel habits during hospitalization. Baseline bowel habits are important to determine adequate bowel function. The change from baseline is more important than the number of bowel movements (Rangwala et al., 2012).
  - (3) Provide privacy and comfort. Inadequate privacy conditions and dependence on a caregiver are directly correlated to risk for constipation (Davies et al., 2020; Larkin et al., 2018.). Avoid using a bedpan when constipation exists (NCI, 2022b).
  - (4) Increase fluid intake to 2,000 ml daily unless contraindicated (NCI, 2022b).
  - (5) Modify diet, as tolerated, to include high-fiber foods, as fiber adds bulk to the stool and assists food in passing more quickly through the stomach and intestines.
    - (a) Insoluble fiber includes wheat bran, fruit and root vegetable skins, whole

**TABLE 15-9.** Pharmacologic Management of Constipation in Adult Patients

| Classification                                             | Mechanism of Action                                                                                                                                                                                              | Drug                                                                                                                                       | Route, Dose, and Schedule                                                                                                                                                                                                                                                                                                                                                                   | Side Effects                                                                                                        | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Opioid-Induced Constipation                                |                                                                                                                                                                                                                  |                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Peripherally acting mu-opioid receptor antagonist (PAMORA) | Peripherally acting mu-opioid antagonist binds with opioid receptors that reverses or prevents opioid-induced constipation without diminishing opioid pain-relieving effects or precipitating opioid withdrawal. | Methylnaltrexone bromide injection (Relistor®)                                                                                             | Dosing for opioid-induced constipation in adult patients with advanced illness: <ul style="list-style-type: none"><li>• 38–62 kg: 8 mg SC</li><li>• 62–114 kg: 12 mg SC</li><li>• If &lt; 38 kg or &gt; 114 kg: 0.15 mg/kg SC</li></ul> Only one dose can be administered in a 24-hour period.<br>Dosing considerations are available for renal and hepatic impairment. See package insert. | Abdominal pain, diarrhea, vomiting, hyperhidrosis, abdominal distension, anxiety, muscle spasms, rhinorrhea, chills | The drug is recommended for patients on opioids with chronic noncancer pain and in adults with advanced illness or pain caused by active cancer.<br>The drug is contraindicated in those with known or suspected mechanical gastrointestinal obstruction and at risk for recurrent obstruction.<br>(Blair, 2019; Salix Pharmaceuticals, 2020)                                                                                                                 |
|                                                            |                                                                                                                                                                                                                  | Naldemedine (Symproic®)                                                                                                                    | Oral: 0.2 mg once daily with or without food                                                                                                                                                                                                                                                                                                                                                | Diarrhea, nausea, abdominal pain, gastroenteritis                                                                   | The drug is only approved for opioid-induced constipation in adults.<br>The drug is contraindicated in those with known or suspected mechanical gastrointestinal obstruction, at increased risk for recurrent obstruction, or with a history of a hypersensitivity reaction to the drug.<br>(Shionogi, 2020)                                                                                                                                                  |
| Bowel Regimen Agents                                       |                                                                                                                                                                                                                  |                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Osmotic laxatives                                          | The sugars or salts create an osmotic gradient in the bowel, leading to water retention, an increase in transit time, and softer stools.                                                                         | Polyethylene glycol (Miralax®)<br>Lactulose<br>Sorbitol<br>Magnesium hydroxide (milk of magnesia)<br>Magnesium citrate<br>Sodium phosphate | Polyethylene glycol (oral): 17 g mixed with 8 oz of liquid, 1–2 times daily<br>Lactulose (oral): 15–30 ml (10–20 g) daily, up to 60 ml daily<br>Sorbitol (oral): 30–150 ml daily<br>Magnesium hydroxide (oral): 30–60 ml daily<br>Magnesium citrate (oral): 148–296 ml daily<br>Sodium phosphate (oral): 15–45 ml daily                                                                     | Bloating, diarrhea, flatulence, nausea, vomiting, epigastric pain                                                   | Administer as a single dose.<br>Oral formulations may be mixed in fruit juice, water, or milk to improve taste.<br>Onset of action may require 48 hours.<br>Adding conventional laxatives may be necessary.<br>Watch for dehydration.<br>Chronic use can lead to altered fluid and electrolyte balance.<br>For sodium phosphate, use caution in patients with renal insufficiency.<br>(McQuade et al., 2016; National Cancer Institute, 2022b; Wickham, 2017) |

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**TABLE 15-9.** Pharmacologic Management of Constipation in Adult Patients (*Continued*)

| Classification                                  | Mechanism of Action                                                                                                                           | Drug                                                       | Route, Dose, and Schedule                                                                                                                        | Side Effects                                                       | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                   |
|-------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Stimulant laxatives                             | Acts directly on the colon to stimulate motility and peristalsis                                                                              | Senna                                                      | Oral 8.6 mg tablets: 1–2 tablets once or twice daily for opioid-induced constipation                                                             | Electrolyte or fluid imbalance with excess catharsis or excess use | Stimulant laxatives are often used as first-line laxatives, particularly for opioid-induced constipation. No evidence shows that adding docusate with senna has any added benefit. Stimulant laxatives are contraindicated in patients with suspected intestinal obstruction or severe dehydration. Overuse of stimulant laxatives can lead to bowel dependence. (McQuade et al., 2016; National Cancer Institute, 2022b; Wickham, 2017) |
|                                                 |                                                                                                                                               | Bisacodyl (Dulcolax®)                                      | Oral: 5–15 mg daily, up to 30 mg daily                                                                                                           | Abdominal cramps or discomfort, diarrhea, proctitis                | The drug should be taken within 2 hours of any other medications. The drug should be avoided for known or suspected ulcerative lesions in the colon. Stimulant laxatives are contraindicated in patients with suspected intestinal obstruction or severe dehydration. Overuse of stimulant laxatives can lead to bowel dependence. (McQuade et al., 2016; National Cancer Institute, 2022b; Wickham, 2017)                               |
| Detergent laxatives and surfactants (softeners) | Direct action on the intestine facilitating water and fats to penetrate into dry stool, which softens the stool and allows for easier passage | Docusate sodium<br>Docusate calcium                        | Docusate sodium (oral): 50–400 mg daily<br>Docusate calcium (oral): 240 mg daily                                                                 | Abnormal and bitter taste in mouth, cramps, diarrhea, nausea       | Increase fluid intake and take with a full glass of fluid with each dose. These agents are often used prophylactically in combination with an oral laxative for individuals at high risk for constipation. (McQuade et al., 2016; National Cancer Institute, 2022b)                                                                                                                                                                      |
| Lubricants                                      | Increases water retention, lubricates the bowel, and softens stool                                                                            | Glycerol suppositories<br>Mineral oil<br>Mineral oil enema | Glycerol suppositories (rectal): 2–3 g suppository for 15 minutes once daily<br>Mineral oil (oral): 10–30 ml daily<br>Mineral oil enema: 1 daily | Perianal irritation                                                | Excessive doses may lead to malabsorption of fat-soluble vitamins. Oral mineral oil should be avoided in individuals with aspiration risk as this can lead to lipid pneumonitis. Avoid giving with additional stool softeners, as this can increase toxicity. (National Cancer Institute, 2022b; Wickham, 2020)                                                                                                                          |

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**TABLE 15-9.** Pharmacologic Management of Constipation in Adult Patients (*Continued*)

| Classification         | Mechanism of Action                                                                                                                 | Drug                                                                                  | Route, Dose, and Schedule                                                   | Side Effects                                                                              | Nursing Considerations                                                                                                                                                                                                                                                                                                                                         |
|------------------------|-------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Bulk-forming laxatives | Causes water to be retained in the bowel, thus increasing the bulk of the stool                                                     | Psyllium<br>Methylcellulose                                                           | Psyllium (oral): 1–3 times daily<br>Methylcellulose (oral): 1–3 times daily | Flatulence, abdominal distension, bloating, mechanical obstruction, anaphylactic reaction | The drug should not be used for patients with established constipation. The drug should not be used for patients with opioid-induced constipation. Bulk-forming laxatives must be taken with 200–300 ml of water to avoid intestinal obstruction and are not an option for patients with poor tolerance of fluids. (Larkin et al., 2018; Wickham, 2017)        |
| Rectal preparations    | Creates an osmotic effect on the intestine, pulling water into the intestines to penetrate dry stool, and also promotes peristalsis | Glycerin suppository<br>Phosphate enema (Fleets®)<br>Sodium citrate enema (Microlax®) | Once daily for suppositories and enemas                                     | Electrolyte imbalances<br>Anal irritation                                                 | Avoid rectal manipulation in patients who are neutropenic. Rectal laxatives and suppositories should be reserved for constipation management when not responding to other interventions and avoided in patients with neutropenia and thrombocytopenia. (Davies et al., 2020; Larkin et al., 2018; National Comprehensive Cancer Network, 2022a; Wickham, 2017) |

SC—subcutaneous



- wheat and whole grains, beans, berries, seeds, and nuts.
- (b) Soluble fiber absorbs liquid to form a gel that eases stool movement and includes fruits, vegetables, beans, barley, and oat bran.
  - (c) Studies have not established specific fiber recommendations for constipation in patients with cancer (NCI, 2022b).
  - (d) A diet high in fiber is not recommended for patients with a current or history of bowel obstruction or who have undergone a colostomy (NCI, 2022b). Obtain a nutrition consult to individualize diet modifications.
- c) Complementary and alternative medicine: Limited evidence exists for using acupuncture to manage constipation in patients with cancer (Rogers et al., 2020). A small body of literature demonstrated that short-term acupressure might be beneficial in treating constipation in patients with advanced cancer (Wang et al., 2019).
8. Patient and family education
- a) Encourage patients to exercise regularly. Regular exercise stimulates GI motility.
  - b) Instruct patients to report constipation and be aware of constipation-associated complications, such as fecal impaction.
  - c) Stress that patients call a physician to initiate a bowel program if three days pass without a bowel movement.
  - d) Ensure that patients prescribed opioids are started on pharmacologic and nonpharmacologic interventions to prevent constipation and maintain the bowel program until opioids are discontinued (Davies et al., 2020; Larkin et al., 2018; NCI, 2022b; NCCN, 2022a, 2022c; Rogers et al., 2020).

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## CHAPTER 16

# Cardiovascular Toxicities

### A. Overview

1. Cardiovascular toxicity is a potential complication of cancer therapy that may result from the direct effects of cancer treatment on heart function and structure or may be due to accelerated development of cardiovascular disease, especially in the presence of traditional cardiovascular risk factors (Chang, Moudgil, et al., 2017; see Table 16-1).
2. Cardiovascular risk factors should be evaluated in all patients starting cardiotoxic cancer therapies.
  - a) Cardiovascular risk factors include cardiovascular disease history, medical risk factors (e.g., diabetes, hypertension, chronic kidney disease), lifestyle risk factors (e.g., smoking, obesity), prior cardiotoxic cancer therapies, and the presence of abnormal cardiac biomarkers (e.g., troponin, brain natriuretic peptide).
  - b) Patients can be stratified for risk of cardiovascular complications based on these factors in conjunction with the specific class of cardiotoxic cancer therapy being initiated (Lyon et al., 2020).
3. Classes of cardiotoxic cancer therapies include chemotherapy agents (e.g., anthracyclines), targeted therapies (e.g., HER2 therapies, vascular endothelial growth factor [VEGF] inhibitors, multitargeted kinase inhibitors, combination rapidly accelerated fibrosarcoma B-type [BRAF] and mitogen-activated protein kinase enzyme [MEK] inhibitors, proteasome inhibitors), and endocrine therapies (e.g., androgen deprivation therapies) and immunotherapies (e.g., immune checkpoint inhibitors, immunomodulatory agents) (Lyon et al., 2020).
4. Novel targeted therapies
  - a) Although novel targeted therapies are considered less toxic and better tolerated by patients than classic chemotherapy agents, rare but serious cardiovascular complications have been described.
  - b) For cancer survivors, the risk of death from cardiovascular causes exceeds that of tumor recurrence for many forms of cancer (Herrmann, 2020; Okwuosa et al., 2017).

5. Side effects: Cardiovascular toxicity encompasses a broad range of cardiovascular side effects related to cancer therapy, including alterations in conduction pathways (e.g., dysrhythmias), vasculature (e.g., hypertension), coronary arteries (e.g., myocardial ischemia), cardiac myocytes (e.g., left ventricular dysfunction, heart failure, myocarditis), pericardial fluid accumulation (e.g., pericardial effusion), and valvular disease (Chang, Okwuosa, et al., 2017; Jain et al., 2017).

### B. Conduction pathway disorders

1. Conduction pathway disorders are disturbances in the regular excitation of the heart (Herrmann, 2020).
2. Conduction disturbances are classified according to origin (e.g., atrial, ventricular) or degree of life-threatening symptoms.
  - a) Sinus dysrhythmias associated with antineoplastic agents usually are transient dysrhythmias, are of short duration, and often are asymptomatic and do not necessitate alteration of the chemotherapy regimen.
  - b) The most commonly observed dysrhythmias associated with cancer treatment include atrial fibrillation and cardiac repolarization abnormalities manifested as QT prolongation and ventricular arrhythmias (e.g., torsades de pointes) (Abu Rmilah et al., 2020; Ganatra et al., 2018; Porta-Sanchez et al., 2017).
3. Atrial fibrillation
  - a) Definition: Atrial fibrillation is the most common of the atrial dysrhythmias and is characterized by an absence of discrete P waves and an “irregularly irregular” ventricular rate that may be caused by factors such as heart disease, hypertension, thyroid problems, and viral infection.
  - b) Pathophysiology: The exact mechanism leading to increased rates of atrial fibrillation in patients with cancer remains unclear; however, it has been suggested that atrial fibrillation may represent an inflammatory complication of cancer (Chu et al., 2019; Ganatra et al., 2018; Herrmann, 2020).

**TABLE 16-1.** Cardiotoxicity of Cancer Therapy

| Classification      | Drug                                     | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|---------------------|------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chemotherapy Agents |                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Alkylating agents   | Busulfan (IV: Busulfex®; oral: Myleran®) | <p>When used in combination with cyclophosphamide</p> <ul style="list-style-type: none"> <li>• Atrial fibrillation</li> <li>• Cardiac dysrhythmia</li> <li>• Complete atrioventricular block</li> <li>• Hypertension (36% with IV formulation)</li> <li>• Left heart failure (with IV formulation)</li> <li>• Pericardial effusion (with IV formulation)</li> <li>• Tachycardia (44% with IV formulation)</li> <li>• Vasodilation (25% with IV formulation)</li> <li>• Ventricular premature heartbeats</li> </ul> <p>Cardiac tamponade (2% with high doses of oral formulation)</p> <p>Chest pain (26% with IV formulation)</p> <p>Pericardial fibrosis (with oral formulation)</p> | Monitor for nausea and vomiting, which often precedes fatal cardiac tamponade. (Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|                     | Cisplatin                                | <p>Bradyarrhythmia</p> <p>Cardiomyopathy (22% with prior chest wall radiation; 5.1% without)</p> <p>Hypertension</p> <p>MI</p> <p>Orthostatic hypotension</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | <p>Before first and subsequent cisplatin treatments, monitor for serum electrolyte disturbances, including hypomagnesemia, hypocalcemia, hyponatremia, hypokalemia, and hypophosphatemia. Maintain normal serum electrolyte levels by supplementation as appropriate.</p> <p>Monitor serum creatinine and blood urea nitrogen levels, which may be elevated in individuals experiencing orthostatic hypotension.</p> <p>Monitor for bradyarrhythmia within 2 hours of starting infusion and up to 3 hours after.</p> <p>Hypertension is associated with combination therapy containing cisplatin, etoposide, vinblastine, and bleomycin. (Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)</p> |
|                     | Cyclophosphamide (high dose)             | <p>Atrial fibrillation</p> <p>Cardiac tamponade</p> <p>Cardiogenic shock</p> <p>Cardiomyopathy</p> <p>Cardiotoxicity (27%; grade 3–4: 3%)</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | <p>Monitor ECG for QTc prolongation in patients treated with high-dose cyclophosphamide-containing chemotherapy. ECG may show diminished QRS complex.</p> <p>Monitor cardiac biomarker B-type (brain) natriuretic peptide in patients on high-dose cyclophosphamide as an indicator of acute heart failure. It can be elevated within the first 24 hours of therapy and remain persistently elevated for up to 1 week after the clinical presentation of acute heart failure.</p>                                                                                                                                                                                                                         |

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**TABLE 16-1.** Cardiotoxicity of Cancer Therapy (*Continued*)

| Classification                        | Drug                                             | Side Effects                                                                                                                                                                                                                                                                                                                      | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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| <b>Chemotherapy Agents (Cont.)</b>    |                                                  |                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Alkylating agents<br>( <i>Cont.</i> ) | Cyclophosphamide (high dose)<br>( <i>Cont.</i> ) | CHF<br>Heart failure (7%–28%)<br>Left ventricular systolic dysfunction<br>MI<br>Myocardial hemorrhage<br>Myocardial necrosis<br>Myocarditis<br>Acute myopericarditis<br>Pericardial effusion (33%)<br>Pericarditis<br>Prolonged QT interval<br>Supraventricular arrhythmia<br>Ventricular fibrillation<br>Ventricular tachycardia | Monitor for cardiotoxicity, including myocarditis, myopericarditis, pericardial effusion, cardiac tamponade, and CHF, which have been reported and may be fatal. The risk for cardiotoxicity increases with high doses, older patients, history of radiation to the chest wall, and previous or current treatment with cardiotoxic agents.<br>Monitor for supraventricular (atrial fibrillation and flutter) and ventricular (tachyarrhythmia associated with severe QT prolongation) arrhythmias.<br>Monitor patients with risk factors and preexisting cardiac disease for cardiotoxicities.<br>Diuretics, angiotensin-converting enzyme inhibitors, and beta-blockers can be initiated if clinically indicated and if no contraindications exist.<br>The spectrum of clinical manifestations from cyclophosphamide-induced cardiotoxicity is variable in presentation and severity. Common manifestations include tachyarrhythmias, hypotension, heart failure, myocarditis, and pericardial disease. These typically present within the first 48 hours of drug administration but may be seen up to 10 days after initiation. Hemorrhagic myocarditis is a rare complication that is uniformly and rapidly fatal.<br>Mild to moderate heart failure and small pericardial effusions generally resolve within a few days to weeks after discontinuation of cyclophosphamide.<br>The risk of cardiotoxicity appears to be dose related (150 mg/kg and 1.5 g/m <sup>2</sup> daily) and occurs 1–10 days after administering the first dose of cyclophosphamide. Higher doses of this drug may produce significant cardiotoxicity, including fatal hemorrhagic myocarditis.<br>Myocardial necrosis may result in rare circumstances.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021) |
|                                       | Dacarbazine                                      | ECG abnormalities<br>Orthostatic hypotension                                                                                                                                                                                                                                                                                      | Monitor blood pressure and observe for ECG abnormalities for patients receiving this therapy.<br>Educate patients about signs and symptoms of hypotension.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                                       | Estramustine (estradiol and nitrogen mustard)    | Cerebrovascular accident<br>CHF<br>Edema (20%)<br>MI<br>Pulmonary embolism                                                                                                                                                                                                                                                        | Monitor for signs and symptoms of CHF (e.g., shortness of breath, lower-extremity edema) and acute MI (e.g., chest pain, shortness of breath, palpitation).<br>Because hypertension may occur, monitor blood pressure periodically.<br>Use estramustine with caution in patients with a history of cerebral vascular or coronary artery disease.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                                       | Ifosfamide (Ifex <sup>®</sup> )                  | Cardiotoxicity (0.5%)<br>Hypotension (0.3%)<br>MI<br>Myocarditis                                                                                                                                                                                                                                                                  | Monitor electrolyte levels.<br>Establish baseline cardiac status and monitor for acute changes.<br>Risk is dose dependent and increased with previous treatment with cardiotoxic agents and regimens, preexisting cardiac disease, renal impairment, and prior irradiation to the cardiac region.<br>Cardiotoxicity includes supraventricular or ventricular arrhythmias, decreased QRS voltage and changes in ST segment or T-wave, toxic cardiomyopathy leading to heart failure, and pericardial effusion, some of which have caused fatalities.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

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**TABLE 16-1.** Cardiotoxicity of Cancer Therapy (*Continued*)

| Classification                        | Drug                               | Side Effects                                                                                                                         | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
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| <b>Chemotherapy Agents (Cont.)</b>    |                                    |                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Alkylating agents<br>( <i>Cont.</i> ) | Melphalan<br>(Adlerian®, Evomela®) | Atrial fibrillation or flutter (11%)<br>Peripheral edema (33%)<br>Supraventricular tachycardia (11%)                                 | Monitor for signs and symptoms of cardiotoxicity, including ECG changes.<br>This drug includes a black box warning for hypersensitivity reactions that may include cardiac arrest.<br>Paroxysmal atrial fibrillation was observed in 5 patients undergoing stem cell transplantation.<br>Supraventricular tachycardia has been associated with longer hospital stays.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                                       | Trabectedin<br>(Yondelis®)         | Cardiomyopathy (all grades: 6%; grade 3–4: 4%)<br>Peripheral edema (all grades: 28%; grade 3–4: 0.8%)                                | Assess neutrophil count, creatine phosphokinase levels, and liver function tests prior to each dose.<br>Assess LVEF by echocardiogram or MUGA scan prior to initiation of therapy.<br>Assess for cardiomyopathy, which may be fatal.<br>Delay next dose for up to 3 weeks in the presence of LVEF < LLN or clinical evidence of cardiomyopathy.<br>Reduce the next dose by 1 dose level for an adverse event during the prior cycle with an absolute decrease of ≥ 10% from baseline to < LLN or clinical evidence of cardiomyopathy.<br>Once dosage has been reduced, it should not be increased in subsequent cycles.<br>Permanently discontinue the drug for symptomatic cardiomyopathy or persistent left ventricular dysfunction that does not recover to LLN within 3 weeks.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Anthracyclines                        | Daunorubicin                       | CHF (50%–80% mortality rate)<br>ECG abnormalities (e.g., ST-T changes)<br>Heart block<br>Supraventricular arrhythmias<br>Tachycardia | Assess for pericarditis and myocarditis, which have been reported with treatment.<br>Monitor cardiac function via ECG or ejection fraction prior to each treatment course and following treatment to assess for acute and late effects.<br><ul style="list-style-type: none"> <li>• During therapy <ul style="list-style-type: none"> <li>– Perform baseline cardiac assessment with an ECG, echo, and, when available, radionuclide angiography (MUGA).</li> <li>– Obtain an echo (or a radionuclide angiogram) before every other subsequent course of therapy with a cumulative dose &lt; 300 mg/m<sup>2</sup>.</li> <li>– Obtain an echo (or a radionuclide angiogram) before each subsequent course of therapy &gt; cumulative dose of 300 mg/m<sup>2</sup> with mediastinal irradiation &lt; 1,000 cGy.</li> <li>– Obtain an echo and radionuclide angiogram before each subsequent course of therapy &gt; a cumulative dose of 300 mg/m<sup>2</sup> with mediastinal irradiation &gt; 1,000 cGy.</li> <li>– Obtain an echo and radionuclide angiogram before each subsequent course of therapy &gt; a cumulative dose of 400 mg/m<sup>2</sup> in the absence of mediastinal irradiation.</li> </ul> </li> <li>• After therapy <ul style="list-style-type: none"> <li>– Obtain an echo at 3–6 months and 12 months after therapy completion. An ECG and radionuclide angiogram should be performed at 1 year following therapy completion.</li> <li>– For patients with healthy cardiac function in the 1-year post-treatment period, a follow-up ECG and echo should be performed every 2–3 years, with a radionuclide angiogram and 24-hour continuous recorded ECG performed every 5 years post-treatment.</li> <li>– For patients with abnormal cardiac function in the 1-year post-treatment period, follow-up ECG and echo should be performed yearly, with a radionuclide angiogram and 24-hour continuous recorded ECG performed every 5 years post-treatment.</li> </ul> </li> </ul> Treatment with anthracycline-based therapy should be avoided for up to 7 months after completing trastuzumab therapy. |

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**TABLE 16-1.** Cardiotoxicity of Cancer Therapy (*Continued*)

| Classification                     | Drug                                           | Side Effects                                                                                                                                                                                                       | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
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| <b>Chemotherapy Agents (Cont.)</b> |                                                |                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Anthracyclines<br>(Cont.)          | Daunorubicin<br>(Cont.)                        |                                                                                                                                                                                                                    | <p>In adults, cardiotoxicity risk is associated with cumulative doses &gt; 400–550 mg/m<sup>2</sup>. Acute or subacute toxicity may occur within 1–23 days after treatment and is not related to cumulative dose, with delayed toxicity occurring months to years after treatment.</p> <p>CHF may be irreversible and resistant to treatment with digitalis.</p> <p>Cardiotoxicity risk increases with a history of radiation to the chest wall, age &gt; 70 years, underlying heart disease or hypertension, and history of or concurrent administration with other anthracyclines or cardiotoxic agents (e.g., trastuzumab).</p> <p>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                                    | Daunorubicin and cytarabine liposome (Vyxeos™) | Cardiac dysrhythmia (30%)<br>Cardiotoxicity (nonconduction related: 20%)<br>Edema (51%)<br>Hypertension (18%)<br>Hypotension (20%)                                                                                 | <p>Assess cardiac function prior to starting the drug and each treatment cycle using an ECG, echo, or MUGA scan.</p> <p>Monitor more frequently if patients are receiving concomitant therapy with other cardiotoxic drugs.</p> <p>Discontinue the use of the drug in the presence of impaired cardiac function unless the benefit outweighs the risk.</p> <p>The drug is not recommended for use in patients with LVEF &lt; normal limits.</p> <p>Cardiotoxicity risk is increased with prior anthracycline-based therapy, chest wall irradiation, and a history of cardiac disease or concomitant use of cardiotoxic drugs.</p> <p>CHF risk is increased with total cumulative nonliposomal daunorubicin doses &gt; 550 mg/m<sup>2</sup>.</p> <p>Avoid using this drug in patients who have reached a cumulative lifetime limit of anthracyclines.</p> <p>Periodic monitoring with an echo or MUGA scan is recommended.</p> <p>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                    | Doxorubicin (Adriamycin®)                      | Cardiogenic shock<br>Cardiomyopathy (1%–20%)<br>CHF (1%–20%)<br>ECG abnormality<br>Heart failure<br>Left ventricular failure (1%–20%)<br>MI<br>Myocarditis<br>Pericarditis<br>Sinus tachycardia<br>Tachyarrhythmia | <p>Assess for arrhythmia, which may occur within hours of therapy and can be life threatening.</p> <p>Assess cardiac function via ECG and evaluate for ST-T wave changes and atrioventricular and bundle branch block.</p> <p>Assess for myocarditis or pericarditis, which may occur during or after therapy.</p> <p>Assess for tachyarrhythmias, including sinus tachycardia, premature ventricular contractions, and ventricular tachycardia.</p> <p>Periodic monitoring with an echo or MUGA scan is recommended.</p> <p>Protect against cardiotoxicity with dexrazoxane in 10:1 ratio of dexrazoxane to doxorubicin. A protective agent is administered by rapid infusion 30 minutes prior to doxorubicin.</p> <p>The National Institute for Occupational Safety and Health recommends using double gloves and a protective gown in the preparation and administration of injections. Prepare in a biosafety cabinet or a compounding aseptic containment isolator; eye/face and respiratory protection may be needed. Prepare compounds in a closed-system drug-transfer device. During administration, if there is a potential that the substance could splash or if the patient may resist, use eye/face protection.</p> <p>Dexrazoxane as a cardioprotectant is not recommended during doxorubicin administration.</p> <p>Avoid use of CYP3A4, CYP2D6, and P-glycoprotein inhibitors and inducers and trastuzumab, which may increase the risk of cardiac dysfunction.</p> <p>This drug is contraindicated in patients with a recent MI (within 4–6 weeks).</p> |

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**TABLE 16-1.** Cardiotoxicity of Cancer Therapy (*Continued*)

| Classification                     | Drug                                             | Side Effects                                            | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
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| <b>Chemotherapy Agents (Cont.)</b> |                                                  |                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Anthracyclines<br>( <i>Cont.</i> ) | Doxorubicin<br>(Adriamycin®)<br>( <i>Cont.</i> ) |                                                         | <p>Cardiotoxicity risk factors include prior or concomitant radiation therapy to the chest wall, previous therapy with other anthracyclines or anthracenediones, and concomitant use of other cardiotoxic drugs. Cardiotoxicity risk is dose dependent.</p> <p>Cumulative doses &gt; 550 mg/m<sup>2</sup> are associated with an increased risk of cardiomyopathy. The maximum recommended cumulative doxorubicin dose in combination with paclitaxel is 340–380 mg/m<sup>2</sup>.</p> <p>Fatal cases of cardiotoxicity have occurred at doses &lt; 400 mg/m<sup>2</sup> (all in combination with concurrent administration of cardiotoxic or hepatotoxic agents); therefore, cardiac monitoring is imperative regardless of dosing.</p> <p>Continuous infusion administration may allow for higher cumulative dosing of &gt; 450 mg/m<sup>2</sup> and have been administered with no observed cardiac abnormalities.</p> <p>Administration using a weekly schedule of 20 mg/m<sup>2</sup> was associated with less cardiac damage than an every-3-week schedule of 60 mg/m<sup>2</sup>.</p> <p>Prior doses of other anthracyclines or anthracenediones should be included when calculating total cumulative doses of doxorubicin.</p> <p>Delayed-onset, dose-related cardiomyopathy is the most common and well-known cardiotoxicity and is likely to be irreversible and unresponsive to treatment.<br/>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)</p> |
|                                    | Doxorubicin liposomal<br>(Doxil®)                | Cardiomyopathy (Kaposi sarcoma: < 1%)<br>CHF (up to 2%) | <p>Assess for a history of cardiovascular disease, which increases the risk for cardiac complications.</p> <p>Assess left ventricular cardiac function via MUGA or ECG at baseline, during therapy, and after discontinuation to assess for acute and delayed toxicities.</p> <p>Cardiotoxicity risk has been observed with cumulative anthracycline doses of 450–550 mg/m<sup>2</sup>.</p> <p>Cardiotoxicity at lower doses may occur in patients who received mediastinal irradiation or patients with preexisting heart disease.</p> <p>Chronic effects seen with cumulative doses approaching 550 mg/m<sup>2</sup> may result in CHF.<br/>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

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**TABLE 16-1.** Cardiotoxicity of Cancer Therapy (*Continued*)

| Classification                     | Drug                      | Side Effects                                                                                                                                                                                                                   | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
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| <b>Chemotherapy Agents (Cont.)</b> |                           |                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Anthracyclines<br>( <i>Cont.</i> ) | Epirubicin<br>(Ellence®)  | Atrioventricular block<br>Bradyarrhythmia<br>Bundle branch block<br>Cardiotoxicity<br>CHF (0.4%–3.3%)<br>Left ventricular cardiac dysfunction (1.4%–2.1%)<br>Phlebitis (3%–10%)<br>Thrombophlebitis<br>Ventricular tachycardia | Monitor for dysrhythmias, including premature ventricular contractions, sinus tachycardia, bradycardia, and heart block.<br>Obtain LVEF at baseline and during treatment with ECG and MUGA scan or echo, especially in patients with risk factors for increased cardiotoxicity. Continued LVEF evaluation is recommended in patients with previous anthracycline or anthracenedione exposure.<br>Avoid concomitant use of cardiotoxic agents unless cardiac function is closely monitored.<br>Active or dormant cardiovascular disease, prior or concomitant radiation to the mediastinal or pericardial area, previous therapy with other anthracyclines or anthracenediones, or concomitant use of other cardiotoxic drugs may increase cardiotoxicity risk.<br>In the adjuvant treatment of breast cancer, the maximum cumulative dose used in clinical trials was 720 mg/m <sup>2</sup> .<br>Cardiotoxicity may occur at lower cumulative doses regardless of whether cardiac risk factors are present.<br>The probability of developing clinically evident CHF is estimated at approximately 0.9% with a cumulative dose of 550 mg/m <sup>2</sup> , 1.6% with 700 mg/m <sup>2</sup> , and 3.3% with 900 mg/m <sup>2</sup> .<br>CHF risk rises rapidly with increasing total cumulative doses > 900 mg/m <sup>2</sup> ; cumulative dose should be exceeded only with extreme caution.<br>High single doses have been associated with acute myocardial ischemia.<br>Myocardial toxicity, manifested in its most severe form by potentially fatal CHF, may occur either during therapy with epirubicin or months to years after termination of therapy.<br>Cardiomyopathy is notably late in onset, occurring 6 months to years after therapy.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021) |
|                                    | Idarubicin<br>(Idamycin®) | Cardiovascular findings<br>• Acute MI<br>• Bundle branch block<br>• CHF<br>• Conduction defects<br>• Heart failure<br>• LVEF abnormalities<br>• Supraventricular extrasystoles<br>• T-wave flattening                          | Monitor cardiac function closely while on treatment.<br>Manifestations include ECG changes, such as ventricular and supraventricular extrasystoles, bundle branch block, T-wave flattening, and conduction defects. Evaluate for anemia and infection prior to and during treatment, which may increase cardiotoxicity risk.<br>Patients receiving concurrent therapy with cardiotoxic agents, including trastuzumab, cyclophosphamide, or paclitaxel, should have cardiac function closely monitored.<br>Hold other cardiotoxic agents during treatment unless the benefit outweighs the risk (e.g., trastuzumab, cyclophosphamide, paclitaxel).<br>Anthracycline use should be held for at least 5 half-lives following treatment with idarubicin, and, if used, cardiac function should be closely monitored.<br>Cardiotoxicities may be worsened by previous treatment with doxorubicin.<br>Cardiotoxicity risk may increase with a history of preexisting heart disease or previous therapy with anthracyclines, anthracenediones, other cardiotoxic agents, and concomitant or previous treatment with chest wall irradiation or drugs that suppress cardiac contractility.<br>The drug may be less cardiotoxic than other agents.<br>CHF has been reported with IV idarubicin when given alone or with cytarabine.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                        |

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**TABLE 16-1.** Cardiotoxicity of Cancer Therapy (*Continued*)

| Classification                     | Drug                      | Side Effects                                                                                                                                                                                                            | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
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| <b>Chemotherapy Agents (Cont.)</b> |                           |                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Anthracyclines<br>(Cont.)          | Mitoxantrone              | Bradyarrhythmia<br>Cardiovascular abnormalities<br>(4%–15%)<br>CHF (2.6%)<br>Edema (10%–30%)                                                                                                                            | Monitor patients for bradyarrhythmia, which has been reported as low as 38 bpm on day 2 of therapy.<br>Establish baseline cardiac function.<br>Monitor cardiac status with ECG. Monitor for cardiac arrhythmias, including decreased LVEF, CHF, tachycardia, ECG changes, and MI (rare).<br>Assess cardiac function and LVEF by physical examination, history, and ECG prior to therapy in all patients and consistently after treatment initiation in patients at elevated risk (e.g., history of anthracycline therapy or mediastinal irradiation, preexisting cardiovascular disease).<br>Cardiotoxicity is observed with prolonged administration and at doses > 80–100 mg/m <sup>2</sup> . Previous treatment with doxorubicin, radiation therapy, or a history of cardiac disease increases risk.<br>Monitor for cardiotoxicity beyond doses of 100 mg/m <sup>2</sup> .<br>The maximum dose is considered 160 mg/m <sup>2</sup> ; cardiotoxicity risk increases with cumulative dose. (Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                           |
| Antimetabolites                    | Azacitidine               | Atrial fibrillation (< 5%)<br>Cardiorespiratory arrest (< 5%)<br>Chest pain (16.4%)<br>CHF (< 5%)<br>Dilated cardiomyopathy (< 5%)<br>Heart failure (< 5%)<br>Hypertension (8.6%)<br>Hypotension (6.8%)<br>Pericarditis | Monitor coadministration with other cardiotoxic medications.<br>Toxicity usually is self-limiting and responds to a drug holiday. (Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                                    | Capecitabine<br>(Xeloda®) | Cardiotoxicity<br>Chest pain<br>Edema (33%)<br>Takotsubo cardiomyopathy<br>Vasospasm                                                                                                                                    | Monitor for MI, ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, ECG changes, and cardiomyopathy, all of which have been observed using this agent.<br>Assess for chest pain, even in patients with no prior history, as it has been observed within the first few doses of capecitabine in combination with other chemotherapy, radiation therapy, or both. Patients may have elevated ST intervals but show no signs of ischemia on ECG or stress echocardiogram.<br>These adverse events may be more common in patients with a prior history of coronary artery disease. Assess for edema, particularly in patients undergoing combination therapy with docetaxel, for whom rates were highest.<br>Interrupt drug if grade 2–3 adverse reactions occur; discontinue drug for grade 4 toxicity.<br>Takotsubo cardiomyopathy is a reversible condition characterized by transient apical and midventricular wall motion; patients may present with radiating chest pain, nausea and vomiting, and shortness of breath. (Truven Health Analytics, 2021; Wolters Kluwer Health, 2021) |

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**TABLE 16-1.** Cardiotoxicity of Cancer Therapy (*Continued*)

| Classification                     | Drug                                      | Side Effects                                                                                                                                                                     | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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| <b>Chemotherapy Agents (Cont.)</b> |                                           |                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Antimetabolites<br>(Cont.)         | Clofarabine<br>(Clolar <sup>®</sup> )     | Edema (12.2%)<br>Hypertension (13%)<br>Hypotension (29%)<br>Pericardial effusion (7.8%)<br>Tachycardia (35%)                                                                     | Monitor for hypotension and tachycardia, which may indicate cytokine release syndrome or systematic inflammatory response syndrome.<br>Monitor cardiac function during the 5 days of clofarabine administration.<br>Evaluate for signs and symptoms of cytokine release and systemic inflammatory response syndrome (e.g., tachypnea, tachycardia, hypotension, pulmonary edema), which can lead to systemic inflammatory response syndrome, capillary leak syndrome, and organ failure.<br>Discontinue drug if hypotension occurs during infusion.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                                    | 5-Fluorouracil<br>(Adrucil <sup>®</sup> ) | Cardiotoxicity (1.2%–18%)<br>• Acute coronary syndrome<br>• Angina pectoris<br>• Cardiogenic shock<br>• Cardiomyopathy<br>• Heart failure<br>• MI<br>• ST-T abnormalities on ECG | Assess for signs and symptoms of an acute coronary syndrome, which may include radiating chest pain, diarrhea, and vomiting.<br>Assess for nausea, vomiting, diaphoresis, and signs of ECG changes with angina; angina pain may occur within hours of receiving a second or third dose but may be associated with the first dose.<br>Assess for angina attacks with rechallenge of the drug.<br>Assess for cardiotoxicities during continuous infusion of the drug.<br>Monitor for ST segment changes on ECG.<br>Withhold treatment if cardiotoxicity occurs.<br>An ECG may be performed prior to each administration.<br>Treatment-induced cardiotoxicity may be treated prophylactically or therapeutically with long-acting nitrates or calcium channel blockers.<br>Patients at higher risk for developing cardiotoxicity include those with heart disease, electrolyte disturbances, or radiation exposure to the heart.<br>The incidence of 5-fluorouracil cardiotoxicity is dependent on dose and schedule.<br>An incidence of 10% has been associated with doses > 800 mg/m <sup>2</sup> daily.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021) |
|                                    | Gemcitabine<br>hydrochloride              | Atrial fibrillation<br>Capillary leak syndrome<br>Cardiac dysrhythmia<br>CHF<br>MI<br>Pericardial effusion<br>Peripheral edema (20%)<br>Vasculitis                               | Monitor for hypotension, particularly in patients with an infusion time of > 60 minutes or more than once per week.<br>Assess for tachypnea, pulmonary crackles, and arterial hypoxemia, which may occur in the presence of atrial fibrillation.<br>Assess for dyspnea, diffuse swelling, weight gain, and hypotension, which may occur in the presence of capillary leak syndrome.<br>Discontinue treatment in the presence of capillary leak syndrome, which may occur in monotherapy or combination therapy.<br>Radiation therapy is not recommended during or within 7 days of infusion.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                    | Pemetrexed<br>(Alimta <sup>®</sup> )      | Chest pain (up to 5%)                                                                                                                                                            | Monitor patients for and educate patients and families about signs and symptoms of chest pain, which have been observed in combination with cisplatin.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

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**TABLE 16-1.** Cardiotoxicity of Cancer Therapy (*Continued*)

| Classification                      | Drug                      | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                                                  | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
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| <b>Chemotherapy Agents (Cont.)</b>  |                           |                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Antimetabolites<br>( <i>Cont.</i> ) | Pentostatin<br>(Nipent®)  | Chest pain (3%–10%)<br>Hypotension (3%–10%)<br>Peripheral edema (3%–10%)                                                                                                                                                                                                                                                                                                                                                                      | Monitor patients for and educate patients and families about signs and symptoms of cardiac complications, which have been observed in patients treated with pentostatin for hairy cell leukemia. (Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Antitumor antibiotics               | Bleomycin<br>(Blenoxane®) | Acute chest pain<br>Arterial thrombosis<br>Cerebrovascular accident<br>Coronary arteriosclerosis<br>Edema (50%)<br>MI<br>Raynaud phenomenon                                                                                                                                                                                                                                                                                                   | Monitor for signs and symptoms of arterial thrombosis, including coronary artery disease and arterial thrombosis, which have been observed in patients receiving combination therapy with vinblastine and cisplatin.<br>Assess for acute chest pain during infusion, as it may indicate pleuropericarditis.<br>Assess for edema, particularly in the hands and feet.<br>Cerebrovascular accident has been noted in combination regimens with bleomycin.<br>Maximum lifetime dose is 400 units, but lower doses are recommended when administered with other cardiotoxic agents or chest irradiation involving the heart.<br>Perform routine monitoring with echo as the maximum tolerated dose is approached.<br>Raynaud phenomenon is observed in monotherapy or combination therapy with vinblastine with or without cisplatin.<br>Combination therapy with cisplatin, vinblastine, and etoposide for germ cell tumors is associated with severe myocardial complications. (Truven Health Analytics, 2021; Wolters Kluwer Health, 2021) |
| Plant alkaloids: taxanes            | Docetaxel                 | Cardiac dysrhythmia (2%–8%)<br>Cardiotoxicity, including left ventricular diastolic dysfunction<br>CHF (2.3% reported in combination therapy with doxorubicin and cyclophosphamide)<br>Fluid retention (6.5%–67%)<br>Hypotension (2% observed in hypersensitivity reactions)<br>Myocardial ischemia (1%–2%)<br>Peripheral edema (18%–34%)<br>Syncope (2%)<br>Vasodilation (27% observed in combination with doxorubicin and cyclophosphamide) | Monitor patients for signs and symptoms of fluid retention, particularly those with preexisting history. Assess cardiac function by ECG and serum concentration of the cardiac neurohormone B-type (brain) natriuretic peptide in patients preparing to undergo therapy with this drug.<br>To reduce the severity of fluid retention, premedicate with corticosteroids for 3 days starting 1 day prior to each dose; in patients with prostate cancer, oral dexamethasone is recommended at 12 hours, 3 hours, and 1 hour before drug administration.<br>A black box warning exists for fluid retention with a median weight gain of 2 kg, with up to 15 kg reported in the presence of multiple drug courses; it may require drug discontinuation. (Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                          |

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**TABLE 16-1.** Cardiotoxicity of Cancer Therapy (*Continued*)

| Classification                               | Drug        | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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| <b>Chemotherapy Agents (Cont.)</b>           |             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Plant alkaloids: taxanes<br>( <i>Cont.</i> ) | Paclitaxel  | Atrial fibrillation (< 1% with severe conduction abnormalities)<br>Atrioventricular block (< 1%)<br>Bradyarrhythmia (3%)<br>Cardiac dysrhythmia (< 1%)<br>Cardiotoxicity (1%–13% in combination with trastuzumab and as monotherapy, respectively)<br>CHF, including cardiac dysfunction and reduction of LVEF<br>Edema (21%)<br>Hypotension (9%–17%)<br>Left ventricular diastolic dysfunction<br>MI<br>Supraventricular tachycardia (< 1%)<br>Ventricular arrhythmia (< 1%) | Obtain a baseline ECG, history and physical, and cardiac assessment before treatment.<br>Monitor vital signs frequently, especially during the first hour of infusion.<br>Perform continuous cardiac monitoring during infusion in patients with a history of serious cardiac conduction abnormalities.<br>Cardiac dysrhythmia may require pacemaker placement.<br>Premedication with corticosteroids plus diphenhydramine and an H <sub>2</sub> antagonist (e.g., famotidine) is recommended, with dosing and route of administration varying based on drug administration.<br>The drug has a black box warning for hypersensitivity reactions, including hypotension, which may be fatal.<br>Asymptomatic bradycardia has been observed during infusion, even in patients with no known cardiac history or risk factors.<br>Patients who have undergone treatment with other anthracyclines may be at increased risk for cardiotoxicity.<br>Ventricular tachycardia and ventricular ectopy have been observed in combination therapy with paclitaxel.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021) |
| Plant alkaloids: vinca alkaloids             | Vinblastine | Angina pectoris (rare)<br>Cardiovascular autonomic neuropathy, including abnormal variations in heart rate and blood pressure<br>ECG abnormalities, potentially associated with coronary ischemia<br>Hypertension<br>MI<br>Raynaud phenomenon                                                                                                                                                                                                                                 | Most presentations are rare, but patients should be monitored for signs and symptoms of cardiac dysfunction, including ECG changes and variations in blood pressure and heart rate.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                                              | Vincristine | Angina pectoris (rare)<br>Cardiovascular autonomic neuropathy, including abnormal variations in heart rate and blood pressure<br>Hypertension<br>Hypotension<br>MI                                                                                                                                                                                                                                                                                                            | Most presentations are rare, but patients should be monitored for signs and symptoms of cardiac dysfunction, including ECG changes and variations in blood pressure and heart rate.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

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**TABLE 16-1.** Cardiotoxicity of Cancer Therapy (*Continued*)

| Classification                                    | Drug                         | Side Effects                                                                                                                                                                                                                                              | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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| <b>Chemotherapy Agents (Cont.)</b>                |                              |                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Plant alkaloids: vinca alkaloids ( <i>Cont.</i> ) | Vinorelbine (Navelbine®)     | MI (rare)                                                                                                                                                                                                                                                 | Most presentations are rare, but patients should be monitored for signs and symptoms of cardiac dysfunction. (Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Miscellaneous                                     | Arsenic trioxide (Trisenox®) | Chest pain (25%)<br>Complete atrioventricular block<br>CHF<br>Edema (40%)<br>Hypertension (10%)<br>Hypotension (25%)<br>Palpitations (10%)<br>Prolonged QT interval (2%–40%)<br>Tachycardia (55%)<br>Torsades de pointes (2.5%)<br>Ventricular arrhythmia | Assess for QT prolongation, torsades de pointes, and complete atrioventricular block, which may be fatal.<br>Assess for a history of QT-prolonging drugs, torsades de pointes, QT-interval prolongation, CHF, current use of potassium-wasting diuretics, conditions resulting in hypokalemia or hypomagnesemia, or current use of drugs that can cause electrolyte abnormalities, as these can worsen QT prolongation.<br>Check 12-lead ECG prior to therapy and hold if QTc is > 500 ms.<br>Check all electrolytes prior to administration of medication and replenish prior to therapy. Potassium should be kept > 4 mEq/L and magnesium > 1.8 mEq/L.<br>Discontinue QT-prolonging agents if possible, and perform frequent cardiac monitoring if not possible.<br>Consider dose adjustment prior to restarting therapy after QTc prolongation occurs.<br>The drug should not be administered unless QTc is < 500 ms. Therapy can be resumed once QTc returns to < 460 ms.<br>QT prolongation with dysrhythmias: Usual onset of QT prolongation > 0.50 ms was 1–4 weeks after treatment. QT prolongation effects may persist up to 8 weeks after therapy.<br>Complete atrioventricular block has been reported with arsenic trioxide.<br>Assess for other causes of dysrhythmias prior to administering the drug. (Truven Health Analytics, 2021; Wolters Kluwer Health, 2021) |
|                                                   | Eribulin (Halaven®)          | Hypotension (5%–10% in adult patients with liposarcoma)<br>Peripheral edema (12%)<br>QTc prolongation                                                                                                                                                     | Monitor for QT prolongation (via ECG) in high-risk patients, including those with CHF, bradyarrhythmias, and electrolyte abnormalities and those using QT-prolonging medications.<br>Monitor for electrolyte abnormalities and correct hypokalemia or hypomagnesemia prior to starting the drug and during its use.<br>Use with caution in patients with congenital long QT syndrome. (Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b>Targeted Therapy Agents</b>                    |                              |                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Small molecule inhibitors                         | Afatinib (Gilotrif®)         | Diastolic dysfunction, including left ventricular dysfunction, and ventricular dilation (2.2% in afatinib-treated patients vs. 0.9% in chemotherapy-treated patients)                                                                                     | Most presentations are rare, but patients should be monitored for signs and symptoms of cardiac dysfunction.<br>Discontinue drug in the presence of symptomatic diastolic dysfunction. (Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

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**TABLE 16-1.** Cardiotoxicity of Cancer Therapy (*Continued*)

| Classification                                | Drug                                  | Side Effects                                                                                                                                                                     | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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| <b>Targeted Therapy Agents (Cont.)</b>        |                                       |                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Small molecule inhibitors<br>( <i>Cont.</i> ) | Alectinib<br>(Alecensa <sup>®</sup> ) | Bradyarrhythmia (8.6%–11%)<br>Edema (30%)<br>Fatal cardiac arrest reported in 1 patient in clinical trials<br>Fatal endocarditis (0.4%)                                          | Monitor patients for signs and symptoms of cardiac dysfunction, particularly bradycardia, which may require dose reduction, pause in therapy, or discontinuation.<br>Monitor heart rate and blood pressure regularly. Advise patients to report any changes in heart or blood pressure medication.<br>Dosing may be reinstated with recovery to asymptomatic bradycardia or a heart rate of at least 60 bpm. Discontinue drug in the presence of recurrent bradycardia.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                               |
|                                               | Axitinib<br>(Inlyta <sup>®</sup> )    | Heart failure (2%; grade 3–4: 1%)<br>Hypertension (40%; grade 3–4: 16%)<br>Hypertensive crisis (< 1%)                                                                            | Monitor patients for signs and symptoms of cardiac dysfunction, particularly heart failure and hypertension, including hypertensive crisis, which may require dose reduction, pause in therapy, or discontinuation.<br>Monitor for hypertension (> 150 mm Hg systolic; > 100 mm Hg diastolic), which has been reported, particularly in patients with renal cell carcinoma. The onset of hypertension occurred at a median of 1 month after treatment initiation, although blood pressure increases have occurred as early as 4 days after initiation.<br>Blood pressure should be well controlled before starting this drug; regularly monitor blood pressure during therapy.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                        |
|                                               | Bortezomib<br>(Velcade <sup>®</sup> ) | Heart disease (15%)<br>Heart failure (5%)<br>Hypertension (6%)<br>Hypotension (12%–15%)<br>Peripheral edema (7%)                                                                 | Closely monitor patients with existing heart disease or risk factors for heart disease during therapy. Assess for cardiac dysfunction, including development or exacerbation of CHF and new-onset decreased LVEF, which have been observed, even in patients with no prior history of cardiac abnormalities.<br>Hypotension, including orthostatic and postural hypotension, has been reported; risk increases with concurrent use of medications that can cause hypotension, a history of syncope, and dehydration. Management may include adjusting antihypertensive medications, hydration, and administering mineralocorticoids (e.g., fludrocortisone) or adrenergic agents (e.g., epinephrine).<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021) |
|                                               | Bosutinib<br>(Bosulif <sup>®</sup> )  | Chest pain (7%–12%)<br>Edema (17%–20%)<br>Hypertension (1% to < 10%)<br>Pericardial effusion (1% to < 10%)<br>Pericarditis (0.1% to < 1%)<br>Prolonged QT interval (1% to < 10%) | Monitor for signs of fluid retention, which may present as pericardial effusion, pleural effusion, pulmonary edema, or peripheral edema.<br>Consider dose reductions or pause in therapy for symptomatic pericardial effusions.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

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**TABLE 16-1.** Cardiotoxicity of Cancer Therapy (*Continued*)

| Classification                                | Drug                                                                                 | Side Effects                                                                                                                            | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
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| <b>Targeted Therapy Agents (Cont.)</b>        |                                                                                      |                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Small molecule inhibitors<br>( <i>Cont.</i> ) | Brigatinib<br>(Alunbrig <sup>®</sup> )                                               | Bradyarrhythmia (5.7%–7.6%)<br>Hypertension (11%–21%)                                                                                   | Assess and control blood pressure prior to the start of therapy; monitoring is recommended, and dose reduction, pause in therapy, or discontinuation may be required.<br>Measure blood pressure 2 weeks after initiation and at least monthly thereafter during use.<br>Measure heart rate regularly throughout treatment and more frequently in patients requiring concomitant therapy known to cause bradycardia.<br>For patients with symptomatic bradycardia (heart rate < 60 bpm), hold the drug until the patient is asymptomatic with resting heart rate of ≥ 60 bpm.<br>If the drug is anticipated to be the primary or monotherapeutic source of bradycardia, resume dosing at the next lowest efficacious level.<br>Permanently discontinue drug if no contributing concomitant medication is identified or if bradycardia is recurrent or unresponsive to therapy.<br>For patients with grade 3 hypertension (systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 100 mm Hg), initiate antihypertensive therapy.<br>Withhold the drug until hypertension has recovered to ≤ grade 1 (systolic blood pressure < 140 mm Hg and diastolic blood pressure < 90 mm Hg), then restart with the next lower dose.<br>If grade 3 hypertension recurs, withhold therapy until recovery to ≤ grade 1 and resume at the next lower dose.<br>Permanently discontinue the drug in the presence of recurrent grade 3 or higher hypertension.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021) |
|                                               | Cabozantinib<br>(capsules: Cometriq <sup>®</sup> ; tablets: Cabometyx <sup>®</sup> ) | Arterial thromboembolism (2%)<br>Hypertension (33%–39%)<br>Hypotension (7%)<br>Pulmonary embolism (4%)<br>Venous thromboembolism (6–7%) | Monitor blood pressure before treatment initiation and regularly during therapy.<br>Discontinue drug in the presence of malignant hypertension, hypertensive crisis, or persistent uncontrolled hypertension despite medical management.<br>Hypertension may require dose reduction, pause in therapy, or discontinuation.<br>Hypertension is one of the most common adverse events leading to dose reduction in patients with renal cell carcinoma.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

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**TABLE 16-1.** Cardiotoxicity of Cancer Therapy (*Continued*)

| Classification                                | Drug                       | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
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| <b>Targeted Therapy Agents (Cont.)</b>        |                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Small molecule inhibitors<br>( <i>Cont.</i> ) | Carfilzomib<br>(Kyprolis®) | Cardiac arrest (> 10% combination therapy; > 20% monotherapy)<br>Chest wall pain (11.4%)<br>CHF (> 10% combination therapy; > 20% monotherapy)<br>Heart failure (> 10% combination therapy; > 20% monotherapy)<br>MI (> 10% combination therapy; > 20% monotherapy)<br>Myocardial ischemia (> 10% combination therapy; > 20% monotherapy)<br>Peripheral edema (16%–20%)<br>Restrictive cardiomyopathy<br>Venous thrombosis (9%–13% combination therapy; 2% monotherapy) | Monitor patients for signs and symptoms of cardiac dysfunction, especially those that may require dose reduction, pause in therapy, or discontinuation.<br>Monitor for volume overload, particularly in patients with risk factors for cardiac failure.<br>Monitor for signs or symptoms of cardiac failure or cardiac ischemia, and evaluate promptly.<br>Hypertension, hypertensive crisis, and hypertensive emergency have been reported and included fatalities; monitoring is recommended, and pause in therapy or discontinuation may be required.<br>Adjust total fluid intake as appropriate in patients with baseline cardiac failure or risk factors for cardiac failure.<br>Withhold treatment for grade 3–4 cardiac adverse events, and consider restarting at a reduced dose after resolution, if appropriate.<br>Risk of cardiac complications increases in individuals aged ≥ 75 years, with New York Heart Association class III–IV heart failure, recent MI, or uncontrolled conduction abnormalities.<br>New or worsening cardiac failure (e.g., CHF, pulmonary edema, decreased LVEF), restrictive cardiomyopathy, myocardial ischemia, and MI have been reported, with potential for fatality.<br>Fatal cardiac arrest within 1 day of carfilzomib administration has been reported.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021) |
|                                               | Ceritinib<br>(Zykadia®)    | Bradyarrhythmia (1%)<br>Cardiac tamponade (rare but can be fatal)<br>Prolonged QT interval (12%)                                                                                                                                                                                                                                                                                                                                                                        | Monitor ECGs and electrolytes in patients treated with QT-prolonging drugs or with concurrent electrolyte abnormalities, bradyarrhythmias, or CHF.<br>Perform periodic ECGs in patients at risk for QT interval prolongation (i.e., CHF, bradyarrhythmias, electrolyte abnormalities, or concomitant QT-prolonging drugs).<br>Advise patients to report any changes in heart or blood pressure medication.<br>Withhold drug in presence of prolonged QT interval until recovery to baseline, then resume with a reduced dose; may require permanent discontinuation if condition persists.<br>Permanently discontinue if QTc interval prolongation occurs with torsades de pointes, polymorphic ventricular tachycardia, or serious arrhythmia.<br>The drug may cause concentration-dependent increases in QTc interval, resulting in increased risk for ventricular tachyarrhythmias (e.g., torsades de pointes) or sudden death.<br>The drug should not be used in patients with congenital long QT syndrome.<br>Monitor heart rate and blood pressure regularly during treatment.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                     |
|                                               | Cobimetinib<br>(Cotellic®) | Cardiomyopathy, including decreased symptomatic or asymptomatic cardiac ejection fraction<br>Hypertension (15%)                                                                                                                                                                                                                                                                                                                                                         | Evaluate LVEF prior to initiation of treatment, 1 month after initiation, and every 3 months thereafter.<br>The drug may require pause of therapy, dose reduction, or discontinuation based on recovery of ejection fraction.<br>When resuming treatment after interruption or dose reduction, monitor LVEF after 2, 4, 10, and 16 weeks and as clinically indicated.<br>The median time to onset was 4 months, and the median time to resolution was 3 months for decreased ejection fraction; resolution often is > LLN or within 10% of baseline.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

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**TABLE 16-1.** Cardiotoxicity of Cancer Therapy (*Continued*)

| Classification                                | Drug                      | Side Effects                                                                                                                                                                                                                                                                                                   | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
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| <b>Targeted Therapy Agents (Cont.)</b>        |                           |                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Small molecule inhibitors<br>( <i>Cont.</i> ) | Crizotinib<br>(Xalkori®)  | Bradyarrhythmia (5%–14%)<br>Edema (31%–49%)<br>Prolonged QT interval (2.1%–6%)                                                                                                                                                                                                                                 | Regularly monitor heart rate and blood pressure.<br>Consider periodic monitoring with ECG and electrolytes in patients with risk factors for QT prolongation.<br>Perform baseline and periodic monitoring of electrolytes with a potassium goal of 4 mEq/L and a magnesium goal of 2 mEq/L.<br>Withhold treatment if symptomatic bradycardia occurs; treatment may be resumed when heart rate is ≥ 60 bpm.<br>Permanently discontinue drug in the presence of life-threatening bradycardia.<br>Use with caution in patients with higher risk of developing prolonged QT interval or with baseline cardiac disease, including congenital long QT syndrome.<br>Interrupt treatment for QTc > 500 ms on at least 2 separate ECGs. May resume at a reduced dose following recovery to QTc ≤ 480 ms.<br>Discontinue use if QTc > 500 ms develops (or a ≥ 60 ms increase from baseline) with torsades de pointes, polymorphic ventricular tachycardia, or signs and symptoms of serious arrhythmia.<br>Edema can intensify with combination treatment with pemetrexed plus cisplatin.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021) |
|                                               | Dabrafenib<br>(Tafinlar®) | Cardiomyopathy (2.9%–6%)<br>Deep vein thrombosis (up to 7%)<br>Peripheral edema (17%–31%)<br>Prolonged QT interval (2%–13%)                                                                                                                                                                                    | Assess LVEF by echo or MUGA scan prior to treatment, 1 month after initiation of treatment, and every 2–3 months following.<br>Monitor for QT prolongation > 500 ms, which has been reported.<br>Cardiomyopathy may require a pause in therapy (reported in 2.4% of patients on monotherapy and 4.4% on combination therapy), dose reduction, or discontinuation (reported in 1% of patients).<br>Withhold treatment for symptomatic cardiomyopathy or asymptomatic left ventricular dysfunction of > 20% from baseline and < LLN.<br>Resume treatment at the same dose level.<br>The median time to onset of cardiomyopathy was 4.4 months (monotherapy) and 8.2 months (combination therapy with dabrafenib plus trametinib).<br>Incidence of deep vein thrombosis and pulmonary embolism is increased when dabrafenib is used in combination with trametinib.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                |
|                                               | Dasatinib<br>(Sprycel®)   | CHF or cardiac dysfunction, including acute cardiac failure, cardiomyopathy, diastolic and left ventricular dysfunction, ventricular failure, and decreases in ejection fraction (2%–4%)<br>Edema (generalized: 1%–4%; localized/superficial: 3%–22%)<br>Palpitations (1%–10%)<br>Pericardial effusion (3%–4%) | Monitor patients for signs and symptoms of cardiac dysfunction, which may require dose reduction, pause in therapy, or discontinuation.<br>Assess for signs and symptoms of fluid retention, which is one of the most commonly reported adverse events, but it appears less frequently with once-daily dosing.<br>Use with caution in patients who have or may develop QTc prolongation (maximum mean change in QTcF from baseline: 7–13.4 ms), including patients with hypokalemia or hypomagnesemia, those who are receiving antiarrhythmic medications or other medications that prolong the QT interval, or those who have had high cumulative doses of anthracyclines.<br>Correct hypokalemia and hypomagnesemia prior to the initiation of therapy.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                                       |

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**TABLE 16-1.** Cardiotoxicity of Cancer Therapy (*Continued*)

| Classification                                | Drug                                        | Side Effects                                                                                                                                                                                                                                                  | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
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| <b>Targeted Therapy Agents (Cont.)</b>        |                                             |                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Small molecule inhibitors<br>( <i>Cont.</i> ) | Dasatinib<br>(Sprycel®)<br>( <i>Cont.</i> ) | Prolonged QT interval (1%)<br>Tachyarrhythmia (1%–10%)<br>Ventricular arrhythmia (< 1%)                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|                                               | Ibrutinib<br>(Imbruvica®)                   | Atrial fibrillation and flutter<br>(6%–9%)<br>Hypertension (6%–17%)<br>Peripheral edema (12%–25%)                                                                                                                                                             | Monitor patients for signs and symptoms of cardiac dysfunction, which may require dose reduction, pause in therapy, or discontinuation.<br>Perform ECG in patients who develop arrhythmic symptoms (e.g., palpitations, light-headedness) or new-onset dyspnea.<br>Conduct periodic clinical monitoring for atrial fibrillation, especially in older adult patients.<br>Monitor for uncontrolled or new-onset hypertension.<br>Atrial fibrillation was one of the most common grade 3–4 nonhematologic adverse reactions in mantle cell lymphoma trials.<br>Incidence of atrial fibrillation is increased in patients with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|                                               | Imatinib mesylate<br>(Gleevec®)             | Cardiac tamponade<br>Cardiogenic shock<br>Chest pain (7%–11%)<br>CHF (up to 1%)<br>Edema<br>Heart failure<br>Hypotension (11%)<br>Palpitations (up to 5.2%)<br>Pericardial effusion<br>Pericarditis<br>Peripheral edema (up to 33%)<br>Tachycardia (up to 1%) | Weigh patients regularly, and monitor for signs and symptoms of fluid volume overload.<br>Monitor for signs and symptoms of cardiac dysfunction, which may require dose reduction, pause in therapy, or discontinuation.<br>Monitor ECG and serum troponin levels for signs and symptoms of hypereosinophilic syndrome and cardiac involvement, which have been associated with cardiogenic shock and left ventricular dysfunction.<br>Assess for CHF in older adult patients and those with a history of coronary disease.<br>Assess for edema, including potential for pleural effusion, pericardial effusion, pulmonary edema, and ascites, with superficial edema most prominent in the lower extremities.<br>In patients with chronic myeloid leukemia, edema risk increases in those receiving high-dose therapy and those > age 65 years.<br>Manage edema with a pause in therapy and diuretic agents.<br>Cardiogenic shock can be reversible when managed with systemic steroids, circulatory support, and interruption of imatinib treatment.<br>Prophylactic concurrent use of systemic steroids 1–2 mg/kg for 1–2 weeks may be indicated if either ECG or troponin is abnormal at the initiation of imatinib therapy.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021) |

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**TABLE 16-1.** Cardiotoxicity of Cancer Therapy (*Continued*)

| Classification                                | Drug                                     | Side Effects                                                                                                                                                                                        | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|-----------------------------------------------|------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Targeted Therapy Agents (Cont.)</b>        |                                          |                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Small molecule inhibitors<br>( <i>Cont.</i> ) | Lapatinib<br>(Tykerb <sup>®</sup> )      | Depression of left ventricular systolic function (1.52%–3.98%; grade 3–4: < 1%)<br>Heart failure<br>Prolonged QT interval<br>Torsades de pointes<br>Variant angina (< 1%)<br>Ventricular arrhythmia | Monitor for signs and symptoms of cardiac dysfunction, particularly QT interval prolongation, and decreased LVEF, which may require dose reduction, pause in therapy, or discontinuation.<br>Confirm normal LVEF before beginning this drug.<br>Obtain baseline cardiac evaluation with an echo or MUGA scan.<br>Assess for prolonged QT interval in patients with hypokalemia or hypomagnesemia, congenital long QT syndrome, concomitant use of antiarrhythmic agents or other agents that lead to QT prolongation, or cumulative high-dose anthracycline therapy.<br>Discontinue treatment in patients with a decreased LVEF ≥ grade 2 and in patients with an LVEF < LLN. May rechallenge at a reduced dose if after 2 weeks the LVEF has recovered to normal and the patient is asymptomatic.<br>Evaluate and correct electrolyte abnormalities prior to the start of and during treatment, specifically hypokalemia and hypomagnesemia, to reduce the risk of prolonged QT interval.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                        |
|                                               | Lenvatinib<br>(Lenvima <sup>™</sup> )    | Hypertension (42%–73%)<br>Hypotension (9%)<br>Myocardial dysfunction (7%–10%)<br>Peripheral edema (21%–42%)<br>Prolonged QT interval (9%–11%)                                                       | Monitor for signs and symptoms of cardiac dysfunction, particularly QT interval prolongation, hypertension, and decreased ventricular function, which may require dose reduction, pause in therapy, or discontinuation.<br>Monitor blood pressure and correct at baseline, prior to treatment, and after 1 week, every 2 weeks for the first 2 months, and then at least monthly thereafter.<br>Monitor ECG in patients with congenital long QT syndrome, CHF, bradyarrhythmias, and concomitant use of drugs that prolong the QT interval (including class Ia and III antiarrhythmics).<br>Monitor for and correct electrolyte abnormalities in all patients.<br>Hold treatment for grade 3 hypertension despite optimal antihypertensive therapy, grade 3 cardiac dysfunction, and QT prolongation > 500 ms. Treatment may be resumed at a reduced dose when hypertension is controlled ≤ grade 2; cardiac dysfunction improves to grade 0, 1, or baseline; or when QT prolongation improves to < 480 ms or baseline.<br>Discontinue treatment in the presence of life-threatening hypertension or grade 4 cardiac dysfunction.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021) |
|                                               | Mobocertinib<br>(Exkivity <sup>™</sup> ) | Atrial fibrillation (1.6%)<br>Heart failure (2.7%),<br>QTc prolongation (10%)                                                                                                                       | Check LVEF at baseline and during treatment.<br>The dose may need to be paused, reduced, or permanently discontinued depending on the severity of the cardiac event.<br>Avoid the concomitant use of other drugs that prolong QTc interval.<br>Avoid the concomitant use of hormone contraceptives.<br>(Takeda Oncology, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

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**TABLE 16-1.** Cardiotoxicity of Cancer Therapy (*Continued*)

| Classification                                | Drug                       | Side Effects                                                                                                                                                                                                                                                                                                     | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
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| <b>Targeted Therapy Agents (Cont.)</b>        |                            |                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Small molecule inhibitors<br>( <i>Cont.</i> ) | Nilotinib<br>(Tasigna®)    | Hypertension (10%–11%)<br>Ischemic heart disease (5%–9.4%)<br>MI (< 1%)<br>Pericardial effusion (< 1%)<br>Peripheral arterial occlusive disease (2.9%–3.6%)<br>Peripheral edema (9%–15%)<br>Prolonged QT interval (< 10%)<br>Sudden death due to cardiotoxicity (0.3%; likely due to ventricular repolarization) | Monitor for signs and symptoms of cardiac dysfunction, particularly QT interval prolongation, which may require dose reduction, pause in therapy, or discontinuation.<br>Assess ECG at baseline, 7 days after treatment initiation, with dose adjustments, and periodically thereafter.<br>Assess lipid profiles and glucose periodically during the first year of treatment and at least once a year with long-term therapy.<br>Evaluate the potential for drug interactions if statin treatment is warranted.<br>Evaluate cardiovascular status at baseline, and monitor risk factors during therapy.<br>Avoid concomitant use with strong CYP3A4 inhibitors because of the risk for prolonged QT intervals.<br>Dose reduction may be necessary if inhibitors must be given, and the QTc should be monitored closely.<br>Instruct patients to avoid eating 2 hours before and 1 hour after administration, as food increases the drug's bioavailability and risk for toxicity.<br>Avoid concomitant use of drugs known to prolong QT interval.<br>Dose modifications are required based on the severity of the adverse reaction.<br>Monitor for and correct hypomagnesemia and hypokalemia to reduce the risk of QT prolongation.<br>The drug has a black box warning for QT interval prolongation that may progress to torsades de pointes; it should be avoided in patients with long QT syndrome, hypokalemia, hypomagnesemia, and QT prolongation, which may be fatal.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021) |
|                                               | Niraparib<br>(Zejula®)     | Hypertension (20%)<br>Palpitations (10%)<br>Peripheral edema (1%–10%)<br>Tachycardia (1%–10%)                                                                                                                                                                                                                    | Monitor for signs and symptoms of cardiac dysfunction, particularly hypertension, which may require dose reduction, pause in therapy, or discontinuation.<br>Monitor blood pressure and heart rate monthly for the first year and periodically thereafter, especially in patients with cardiovascular disorders (e.g., coronary insufficiency, cardiac arrhythmias, hypertension).<br>Administer antihypertensives, which may require dose adjustment of niraparib.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|                                               | Osimertinib<br>(Tagrisso®) | Cardiomyopathy (1.9%)<br>Decreased cardiac ejection fraction (4%)<br>Prolonged QT interval (0.7%)                                                                                                                                                                                                                | Monitor for signs and symptoms of cardiac dysfunction, particularly QTc prolongation and cardiomyopathy, which may require dose reduction, pause in therapy, or discontinuation.<br>Assess for cardiomyopathies, including cardiac failure, CHF, decreased LVEF, or pulmonary edema, which may be fatal.<br>Closely monitor patients with congenital long QT syndrome, CHF, electrolyte abnormalities, or concomitant use of medications that can prolong the QTc interval, and discontinue therapy in the presence of life-threatening arrhythmia.<br>Permanently discontinue therapy in patients with symptomatic CHF or persistent, asymptomatic left ventricular dysfunction that does not resolve within 4 weeks.<br>Assess LVEF at baseline and every 3 months following with echo or MUGA.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

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**TABLE 16-1.** Cardiotoxicity of Cancer Therapy (*Continued*)

| Classification                                | Drug                    | Side Effects                                                                                                                                                                                                                                                                              | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
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| <b>Targeted Therapy Agents (Cont.)</b>        |                         |                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Small molecule inhibitors<br>( <i>Cont.</i> ) | Panobinostat (Farydak*) | Cardiac dysrhythmia (12%)<br>ECG T-wave abnormalities (40%)<br>Hemorrhage (grade 3–4: 4%)<br>Hypertension (< 10%)<br>Hypotension (< 10%)<br>MI (< 4%)<br>Orthostatic hypotension (< 10%)<br>Palpitations (< 10%)<br>Peripheral edema (29%)<br>ST-segment depression (22%)                 | Monitor for signs and symptoms of cardiac dysfunction, particularly cardiac dysrhythmias, which may require dose reduction, pause in therapy, or discontinuation.<br>Monitor electrolytes during treatment and correct abnormalities as clinically indicated.<br>Assess for ECG changes, including ST-segment depression and T-wave abnormalities and prolongation of cardiac ventricular repolarization (QT interval).<br>Do not initiate therapy in patients with recent MI or unstable angina, a QTcF > 450 ms, or clinically significant baseline ST-segment or T-wave abnormalities.<br>Avoid concomitant use with antiarrhythmics (e.g., amiodarone, disopyramide, procainamide, quinidine, sotalol) or drugs known to prolong the QT interval (e.g., bepridil, chloroquine, clarithromycin, halofantrine, methadone, moxifloxacin, pimozide).<br>Obtain an ECG at baseline and periodically to monitor for abnormalities.<br>The drug has a black box warning for severe and fatal cardiac ischemic events, including severe arrhythmias, and ECG changes that may be exacerbated by electrolyte abnormalities.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021) |
|                                               | Pazopanib (Votrient*)   | Bradyarrhythmia (2%–19%)<br>Chest pain (5%–10%)<br>CHF (1%)<br>Heart failure<br>Hypertension (40%; grade 3–4: 4%–7%)<br>Left ventricular cardiac dysfunction (0.6%–8%)<br>MI (2%)<br>Peripheral edema (14%; grade 3: 2%)<br>Prolonged QT interval (0.2%–2%)<br>Torsades de pointes (< 1%) | Perform baseline and periodic monitoring of electrolytes with a potassium goal of 4 mEq/L and a magnesium goal of 2 mEq/L.<br>Control preexisting hypertension before beginning pazopanib therapy.<br>Monitor for cardiac dysfunction, including signs and symptoms of CHF and decreased LVEF, and QT prolongation.<br>Consider periodic monitoring with ECG in patients with risk factors for QT prolongation.<br>Use with caution in patients with a higher risk of developing prolonged QT interval or with baseline cardiac disease.<br>Dose reduction is permitted if hypertension persists despite supportive antihypertensive therapies; persistent or severe hypertension may require discontinuation of therapy.<br>Avoid use of pazopanib in patients with a recent (within 6 months) arterial thromboembolic event.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                         |

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**TABLE 16-1.** Cardiotoxicity of Cancer Therapy (*Continued*)

| Classification                                | Drug                    | Side Effects                                                                                                                                                                                                                                                                                                | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
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| <b>Targeted Therapy Agents (Cont.)</b>        |                         |                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Small molecule inhibitors<br>( <i>Cont.</i> ) | Ponatinib<br>(Iclusig®) | Arterial ischemia (11%–42%)<br>Atrial fibrillation (7%)<br>Bradyarrhythmia (1%)<br>Cardiac dysrhythmia (19%)<br>Heart failure (6%–15%)<br>Hypertension (53%–71%)<br>Myocardial ischemia (21%)<br>Peripheral artery occlusive disease (12%)<br>Peripheral edema (13%–22%)<br>Venous thromboembolism (4%–10%) | <p>Monitor for signs and symptoms of cardiac dysfunction, particularly cardiac ischemia, infarction, or hypertension, which may require dose reduction, pause in therapy, or discontinuation.</p> <p>Assess patients with hypertension for confusion, headache, chest pain, or shortness of breath, which may require urgent clinical intervention.</p> <p>Frequently assess and manage blood pressure prior to and during treatment.</p> <p>Hold therapy to evaluate patients with signs and symptoms of abnormal heart rate, including rapid heart rate in the presence of atrial fibrillation and slow heart rate in the presence of bradyarrhythmia.</p> <p>Interrupt treatment and consider evaluating for renal artery stenosis if significant worsening, labile, or treatment-resistant hypertension occurs.</p> <p>Cardiac vascular occlusions requiring revascularization procedures have occurred, including life-threatening and fatal MI and coronary artery occlusion.</p> <p>Interrupt or discontinue treatment immediately if arterial occlusion is suspected.</p> <p>Consider risks versus benefits before restarting therapy.</p> <p>The drug has a black box warning for arterial occlusion (i.e., MI, stroke, stenosis of large arteries of the brain, severe peripheral vascular disease), venous occlusive events, and life-threatening or fatal heart failure and left ventricular dysfunction.</p> <p>Arterial ischemia includes cardiovascular, cerebrovascular, and peripheral vascular ischemia.</p> <p>Atrial fibrillation was the most common arrhythmia reported during clinical trials, and approximately 50% of cases were grade 3–4.</p> <p>Additional grade 3–4 arrhythmia events included syncope, tachycardia, bradycardia, QT prolongation, atrial flutter, supraventricular tachycardia, ventricular tachycardia, atrial tachycardia, complete atrio-ventricular block, cardiorespiratory arrest, loss of consciousness, and sinus node dysfunction, with some patients requiring hospitalization.</p> <p>Fatal and life-threatening arterial occlusions may occur within 2 weeks of initiation and at dosages as low as 15 mg daily; median time to first onset is 193 days, so monitoring should be long term for these patients.</p> <p>Risk factors include hypertension, hyperlipidemia, and preexisting cardiac disease. Event frequency increased with age. Occlusions also occurred in patients without cardiovascular risk factors and in patients aged ≤ 50 years.</p> <p>Peripheral arterial occlusive events requiring revascularization procedures have occurred, including fatal mesenteric artery occlusion and life-threatening peripheral arterial disease. Digital or distal extremity necrosis requiring amputation has also occurred.</p> <p>The median time to onset of the first peripheral vascular arterial occlusive event was 478 days. (Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)</p> |

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**TABLE 16-1. Cardiotoxicity of Cancer Therapy (Continued)**

| Classification                         | Drug                       | Side Effects                                                                                                                                                                                                                                  | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
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| <b>Targeted Therapy Agents (Cont.)</b> |                            |                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Small molecule inhibitors<br>(Cont.)   | Regorafenib<br>(Stivarga®) | Hypertension (30%–59%; grade 3–4: 8%–28%)<br>Hypertensive crisis (0.25%)<br>MI (1.2%)<br>Myocardial ischemia (1.2%)                                                                                                                           | Patients should be monitored for signs and symptoms of cardiac dysfunction, particularly cardiac ischemia, infarction, or hypertension, which may require dose reduction, pause in therapy, or discontinuation. Blood pressure should be adequately controlled prior to initiation of the drug and monitored weekly for the first 6 weeks during therapy, then at least every cycle. The drug should be temporarily withheld or permanently discontinued in patients with severe or uncontrolled hypertension.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|                                        | Ribociclib<br>(Kisqali®)   | Peripheral edema (12%)<br>Prolonged QT interval (3%)<br>Sudden cardiac death (0.3%)<br>Syncope (2.7%)                                                                                                                                         | Monitor for signs and symptoms of cardiac dysfunction, particularly prolongation of QT interval, electrolyte imbalances, and syncope, which may require dose reduction, pause in therapy, or discontinuation. Assess ECG prior to initiation, during therapy, and as clinically indicated, as ECG changes have been observed within the first 4 weeks of treatment and were reversible with dose interruption. Monitor serum potassium, calcium, phosphorus, and magnesium prior to initiation, during therapy, and as clinically indicated. Prolongation of the QT interval, which is drug concentration–dependent, can result in sudden death. Avoid use of ribociclib in patients with preexisting QT prolongation or those at risk (e.g., long QT syndrome, recent MI, CHF, unstable angina, bradyarrhythmias). Avoid concomitant use of drugs known to prolong the QT interval. Correct any electrolyte abnormalities prior to starting therapy to avoid QT prolongation.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021) |
|                                        | Romidepsin<br>(Istodax®)   | ECG changes (QT prolongation)<br>ECG ST-segment changes (2%–63%)<br>Hypotension (7%–23%)<br>QTc prolongation (at least 2%)<br>Supraventricular arrhythmia (6%)<br>Ventricular arrhythmia (4%)                                                 | Monitor international normalized ratio more frequently in patients receiving concurrent warfarin therapy. ECG changes, including T-wave and ST-segment changes, have been reported; prior to administration, confirm that potassium and magnesium levels are within normal limits. Monitor for ECG changes in patients with congenital long QT syndrome, a history of significant cardiovascular disease, or concomitant use of antiarrhythmic or QT-prolonging agents, for whom these risks are elevated. Obtain baseline and periodic ECGs. Monitor for and correct electrolyte abnormalities.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                                                                                               |
|                                        | Sorafenib<br>(Nexavar®)    | Cardiac dysrhythmia (< 1%)<br>CHF (1.9%)<br>Edema<br>Heart failure exacerbation<br>Hypertension (19.1%; grade 3–4: 4.3%)<br>Hypertensive crisis (< 1%)<br>MI (1.9%–2.9%)<br>Myocardial ischemia (1.9%–2.9%)<br>Prolonged QT interval (< 0.1%) | Monitor for signs and symptoms of cardiac dysfunction, particularly cardiac ischemia, hypertension, and MI, which may require dose reduction, pause in therapy, or discontinuation. Monitor for QT interval prolongation in patients with CHF, bradyarrhythmias, electrolyte abnormalities, and concomitant use of other drugs known to prolong the QT interval. Monitor blood pressure weekly for the first 6 weeks of treatment, then every 2–3 weeks for the duration of treatment. Avoid use in patients with congenital long QT syndrome. Hypertension can be severe and potentially persistent. Treat preexisting hypertension with standard hypertensive agents before treatment initiation. In the presence of prolonged QT interval, monitor ECGs and electrolytes (i.e., magnesium, calcium, potassium) in at-risk patients, and interrupt treatment with QTc interval > 500 ms or increases from baseline ≥ 60 ms.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                  |

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**TABLE 16-1.** Cardiotoxicity of Cancer Therapy (*Continued*)

| Classification                                | Drug                       | Side Effects                                                                                                                                                                                                                                                             | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
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| <b>Targeted Therapy Agents (Cont.)</b>        |                            |                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Small molecule inhibitors<br>( <i>Cont.</i> ) | Sunitinib<br>(Sutent®)     | Aortic dissection (rare but potentially fatal)<br>Heart failure (up to 2%)<br>Hypertension (15%–39%)<br>Left ventricular cardiac dysfunction (11%–27%)<br>Peripheral edema (10%–24%)<br>Prolonged QT interval<br>Thromboembolic disorder<br>Torsades de pointes (< 0.1%) | Monitor for signs and symptoms of cardiac dysfunction, particularly CHF and hypertension, which may require dose reduction, pause in therapy, or discontinuation.<br>Monitor for cardiotoxicity (e.g., myocardial disorders, cardiomyopathy), especially in patients with a history of cardiac events, pulmonary embolism, cerebrovascular accident, or transient ischemic attack.<br>Monitor for LVEF 20%–50% below baseline, which may occur without clinical evidence of CHF; monitoring is recommended.<br>Patients with a history of QT interval prolongation, relevant preexisting cardiac disease, bradycardia, electrolyte disturbances, or concomitant use of antiarrhythmics or strong CYP3A4 inhibitors may experience QT interval prolongation and torsades de pointes.<br>Obtain baseline LVEF prior to initiation of the drug, especially in patients with cardiac risk factors.<br>Monitor for and correct hypomagnesemia and hypokalemia to reduce the risk of QT prolongation.<br>Monitor blood pressure weekly for the first 6 weeks, then periodically throughout therapy. Standard antihypertensive agents are recommended for the management of hypertension.<br>Therapy breaks have been effective for the resolution of hypertension.<br>Hypertension seems to be related to the presence of proteinuria, and both usually are present prior to cardiac failure.<br>Halt all therapy if symptomatic myocardial ischemia or manifestations of CHF occur temporally related to drug administration.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021) |
|                                               | Temsirolimus<br>(Torisel®) | Chest pain (16%)<br>Edema (35%)<br>Hypertension (7%)<br>Venous thromboembolism (2%)                                                                                                                                                                                      | Assess for angioedema, which has been reported when taken in combination with angiotensin-converting enzyme inhibitors or calcium channel blockers.<br>Monitor for signs and symptoms of angioedema and elevations in blood pressure.<br>Treatment-induced or intensified hypertension may require management with one or more antihypertensive agents.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|                                               | Tivozanib<br>(Fotivda®)    | Arterial thromboembolic events (2.9%)<br>Cardiac failure<br>Cardiac ischemia<br>Hypertension (> 20%)<br>Hypertensive crisis<br>Venous thromboembolic events (3.5%)                                                                                                       | Control blood pressure prior to starting treatment and treat high blood pressure during treatment with antihypertensive agents.<br>Consider dose reduction for uncontrolled hypertension.<br>Permanently discontinue for severe arterial (e.g., MI, stroke) or venous thromboembolic events.<br>(AVEO Pharmaceuticals, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

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**TABLE 16-1.** Cardiotoxicity of Cancer Therapy (*Continued*)

| Classification                                | Drug                      | Side Effects                                                                                                                      | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
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| <b>Targeted Therapy Agents (Cont.)</b>        |                           |                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Small molecule inhibitors<br>( <i>Cont.</i> ) | Trametinib<br>(Mekinist®) | Bradyarrhythmia (up to 10%)<br>Cardiomyopathy (6%–9%)<br>Hypertension (15%–26%)<br>Peripheral edema                               | <p>Monitor for signs and symptoms of cardiac dysfunction, which may require dose reduction, pause in therapy, or discontinuation.</p> <p>Assess LVEF by echo or MUGA scan before initiating treatment, 1 month after initiation, and at 2–3-month intervals thereafter during therapy.</p> <p>Monitor for cardiomyopathy, defined as a decrease in LVEF below the institutional LLN with an absolute decrease in LVEF &gt; 10% below baseline, which has occurred with the use of this drug in monotherapy and combination regimens.</p> <p>The median time to onset of cardiomyopathy was 2.1 months with monotherapy and 6.7–8.2 months with combination therapy; therefore, patients should have long-term monitoring for this toxicity.</p> <p>Withhold treatment in patients with LVEF &gt; 10% below baseline; however, treatment may be resumed at a lower dosing level if LVEF improves to normal value.</p> <p>Permanently discontinue treatment for symptomatic cardiomyopathy or persistent, asymptomatic LVEF dysfunction (&gt;20% decrease from baseline and &lt; LLN) that does not resolve within 4 weeks. (Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                               | Vandetanib<br>(Caprelsa®) | Heart failure (0.9%)<br>Hypertension (all grades: 33%; grades 3–4: 5%)<br>Prolonged QT interval (all grades: 14%; grades 3–4: 8%) | <p>Monitor for and correct hypocalcemia, hypomagnesemia, and hypokalemia to reduce risk of QT prolongation. Correct these electrolyte abnormalities prior to treatment initiation.</p> <p>Monitor for QT prolongation, torsades de pointes, ventricular tachycardia, and sudden death at baseline, during initiation of treatment, and at dose escalation.</p> <p>Therapy is contingent on QTc; treatment should not be initiated if &gt; 450 ms.</p> <p>If QTcF interval &gt; 500 ms during therapy, temporarily discontinue therapy, and then resume at a reduced dose.</p> <p>Hold drug in the presence of <i>Common Terminology Criteria for Adverse Events</i> ≥ grade 3 toxicity; resume at a reduced dose.</p> <p>Heart failure and hypertension, including hypertensive crisis, have been reported, which may require holding, dose modifying, or discontinuing the drug.</p> <p>Do not use in patients with a history of or active torsades de pointes, bradyarrhythmias, or uncompensated heart failure.</p> <p>Use is contraindicated in patients with congenital long QT syndrome.</p> <p>Avoid concomitant use of drugs that prolong QT interval (e.g., clarithromycin, chloroquine, dolasetron, granisetron, haloperidol, methadone, moxifloxacin, pimozide), or perform more frequent ECG monitoring if use is necessary.</p> <p>This medication is available through a Risk Evaluation and Mitigation Strategy (REMS) program. Both prescribers and pharmacies must be certified with the program to prescribe and dispense the drug. (National Cancer Institute Cancer Therapy Evaluation Program, 2017; Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)</p> |

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**TABLE 16-1.** Cardiotoxicity of Cancer Therapy (*Continued*)

| Classification                                | Drug                          | Side Effects                                                                                                                                                                 | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|-----------------------------------------------|-------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Targeted Therapy Agents (Cont.)</b>        |                               |                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Small molecule inhibitors<br>( <i>Cont.</i> ) | Vemurafenib<br>(Zelboraf®)    | Atrial fibrillation (< 10%)<br>Cardiac tamponade<br>Hypertension (36%)<br>Peripheral edema (17%–23%)<br>Prolonged QT interval (55%)<br>Vasculitis (< 10%)                    | To reduce risk of QT prolongation, monitor for and correct hypocalcemia, hypomagnesemia, and hypokalemia.<br>Obtain ECGs at baseline, 15 days after the start of treatment, monthly during the first 3 months of treatment, and then at least every 3 months.<br>Assess for QT prolongation, which may increase the risk of torsades de pointes and other ventricular arrhythmias.<br>Hold treatment in patients with uncorrectable electrolyte abnormalities, corrected QT interval of > 500 ms, congenital long QT syndrome, or concomitant use of products known to prolong the QT interval.<br>Withhold treatment in patients who develop grade 3 corrected QT interval prolongation (i.e., more than 500 ms). May restart at a reduced dose in patients who improve to corrected QT interval prolongation ≥ grade 2 (i.e., ≤ 500 ms).<br>Permanently discontinue treatment if QTc remains > 500 ms and > 60 ms higher than baseline values (after controlling for electrolyte abnormalities, CHF, bradyarrhythmias, or other cardiac risk factors).<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021) |
|                                               | Vorinostat<br>(Zolinza®)      | MI<br>Peripheral edema (12.8%)<br>Prolonged QT interval<br>Pulmonary embolism (5%)<br>Syncope                                                                                | Monitor electrolytes, including potassium, magnesium, and calcium, every 2 weeks during the first 2 months of therapy and then monthly, and more frequently in symptomatic patients (e.g., with nausea, vomiting, diarrhea, fluid imbalance, or cardiac symptoms).<br>Teach patients methods to reduce risk of venous thromboembolism: drink fluids and maintain mobility.<br>Consider thromboprophylaxis for patients with additional risks for venous thromboembolism.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|                                               | Zanubrutinib<br>(Brukinsa®)   | Cardiac arrhythmias (e.g., atrial fibrillation, atrial flutter) (3.2%),<br>Hypertension (12%)                                                                                | Patients with hypertension, cardiac history, and acute infection may be at increased risk for arrhythmias.<br>Monitor for signs and symptoms of arrhythmias and treat appropriately.<br>(BeiGene USA, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                               | Ziv-aflibercept<br>(Zaltrap®) | Angina pectoris<br>Decreased ejection fraction<br>Heart failure<br>Hypertension (41%; grade 3: 19%; grade 4: 0.2%)<br>Pulmonary embolism (5%)<br>Venous thromboembolism (9%) | Monitor for signs and symptoms of cardiac dysfunction, which may require dose reduction, pause in therapy, or discontinuation.<br>Monitor blood pressure every 2 weeks or more frequently as indicated.<br>Treat with appropriate antihypertensive therapy.<br>Hold dosing if recurrent or severe hypertension occurs, and restart at a lower dose once blood pressure is controlled.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

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**TABLE 16-1.** Cardiotoxicity of Cancer Therapy (*Continued*)

| Classification                                   | Drug                      | Side Effects                                                                                                                                                                                                        | Nursing Considerations                                                                                                                                                                                                                                                                                                           |
|--------------------------------------------------|---------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Immunotherapy Agents</b>                      |                           |                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                  |
| Checkpoint inhibitors                            | Atezolizumab (Tecentriq®) | Myocarditis<br>Peripheral edema                                                                                                                                                                                     | Myocarditis has been reported, which may necessitate pause in therapy, discontinuation, or prescribing corticosteroids and other immunosuppressive medications. (Wolters Kluwer Health, 2021)                                                                                                                                    |
|                                                  | Avelumab (Bavencio®)      | Hypertension (13%)<br>Myocarditis (<1%)<br>Pericarditis (<1%)<br>Peripheral edema (20%)<br>Vasculitis (<1%)                                                                                                         | Incidences of myocarditis, pericarditis, and vasculitis have occurred. The median time to a major cardiac event is 4.2 months. Optimize cardiovascular risk factors, such as hypertension, diabetes, and hyperlipidemia. (Wolters Kluwer Health, 2021)                                                                           |
|                                                  | Cemiplimab (Libtayo®)     | Hypertension (11%)<br>Myocarditis (<1%)<br>Pericarditis (<1%)<br>Vasculitis (<1%)                                                                                                                                   | Myocarditis has been reported, which may necessitate pause in therapy, discontinuation, or prescribing corticosteroids and other immunosuppressive medications. (Wolters Kluwer Health, 2021)                                                                                                                                    |
|                                                  | Durvalumab (Imfinzi®)     | Peripheral edema (< 10%)<br>Myocarditis (< 1%)<br>Pericarditis (< 1%)<br>Vasculitis (< 1%)                                                                                                                          | Myocarditis has been reported, which may necessitate pause in therapy, discontinuation, or prescribing corticosteroids and other immunosuppressive medications. (Wolters Kluwer Health, 2021)                                                                                                                                    |
|                                                  | Ipilimumab (Yervoy®)      | Heart failure with reduced ejection fraction<br>Myocarditis (severe or fatal: 0.2%)<br>Pericarditis (severe or fatal: 0.2%–1%)                                                                                      | Monitor for signs and symptoms of heart failure, including reduced ejection fraction. Steroid therapy (1–2 mg/kg daily) may be used in the presence of immune-mediated myocarditis and pericarditis; however, severe presentation may require drug discontinuation. (Truven Health Analytics, 2021; Wolters Kluwer Health, 2021) |
|                                                  | Pembrolizumab (Keytruda®) | Acute MI (2%)<br>Cardiac arrhythmia (4%–11%)<br>Cardiac tamponade (2%)<br>Ischemic heart disease (2%)<br>Pericardial effusion (2%)<br>Pericarditis (2%–4%)<br>Peripheral edema (11%–15%)<br>Pulmonary embolism (2%) | Myocarditis has been reported, which may necessitate pause in therapy, discontinuation, or prescribing corticosteroids and other immunosuppressive medications. (Wolters Kluwer Health, 2021)                                                                                                                                    |
| Chimeric anti-gen receptor T-cell immuno-therapy | Axicabtagene (Yescarta®)  | Hypertension (13%–15%)<br>Hypotension (51%–57%)<br>Tachycardia (44%–57%)<br>Thrombosis (10%–12%)                                                                                                                    | Monitor for cytokine release syndrome. The median time to onset is 2–4 days. Presentation may include hypotension, tachycardia, and cardiac arrhythmias. (Wolters Kluwer Health, 2021)                                                                                                                                           |

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**TABLE 16-1.** Cardiotoxicity of Cancer Therapy (*Continued*)

| Classification                                                    | Drug                                                          | Side Effects                                                                                                                                                                                                             | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|-------------------------------------------------------------------|---------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Immunotherapy Agents (Cont.)</b>                               |                                                               |                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Chimeric anti-gen receptor T-cell immuno-therapy ( <i>Cont.</i> ) | Brexucabtagene autoleucel (Tecartus®)                         | Edema (35%)<br>Hypertension (18%)<br>Hypotension (57%)<br>Tachycardia (45%)<br>Thrombosis (17%)                                                                                                                          | Monitor for cytokine release syndrome. The median time to onset is 3 days. Presentation may include hypotension, tachycardia, and cardiac arrhythmias. (Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                         |
|                                                                   | Idecabtagene vicleucel (Abecma®)                              | Edema (25%)<br>Hypertension (11%)<br>Hypotension (17%)<br>Tachycardia (19%)                                                                                                                                              | Monitor for cytokine release syndrome. The median time to onset is 1 day. Presentation may include hypotension, tachycardia, and cardiac arrhythmias. (Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                          |
|                                                                   | Lisocabtagene maraleucel (Breyanzi®)                          | Edema (21%)<br>Hypertension (14%)<br>Hypotension (26%)<br>Tachycardia (25%)                                                                                                                                              | Monitor for cytokine release syndrome. The median time to onset is 5 days. Presentation may include hypotension, tachycardia, cardiac arrhythmias, cardiac arrest, or cardiac failure. (Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                         |
|                                                                   | Tisagenlecleucel (Kymriah®)                                   | Edema (21%)<br>Hypertension (19%)<br>Hypotension (31%)<br>Tachycardia (26%)                                                                                                                                              | Monitor for cytokine release syndrome. The median time to onset is 3 days. Presentation may include hypotension, tachycardia, cardiac arrhythmias, or cardiac dysfunction. (Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                     |
| Colony-stimulating factors                                        | Epoetin alfa (Procrit®)                                       | Cardiovascular events (14%–18%), including MI and stroke<br>CHF (6.6%–9%)<br>Edema (1%–3%)<br>MI (0.8%–2.8%)<br>Hypertension (incidence varies based on indication; surgery: 3%–6%; chronic kidney disease: 13.7%–27.7%) | Monitor for hemoglobin rate increase of > 1 g/dl over a 2-week period, which may increase the risk for death, MI, stroke, and CHF.<br>Use the lowest dose sufficient to reduce the need for blood transfusions.<br>Reduce or withhold dosing if blood pressure cannot be therapeutically controlled.<br>The drug has a black box warning that it may increase the risk of serious cardiovascular and thrombo-embolic events.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021) |
|                                                                   | Filgrastim (granulocyte–colony-stimulating factor; Neupogen®) | Capillary leak syndrome<br>Chest pain (13%)<br>Hypertension (≥ 5%)<br>Syncope (resulting in loss of consciousness: 15%)                                                                                                  | Assess for signs and symptoms of capillary leak syndrome, including hypotension, hypoalbuminemia, edema, and hemoconcentration, as this presentation may be life threatening.<br>In the presence of capillary leak syndrome, which may be life threatening, discontinue the drug and initiate methylprednisolone.<br>Capillary leak syndrome may require management in the intensive care setting.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                           |

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**TABLE 16-1.** Cardiotoxicity of Cancer Therapy (*Continued*)

| Classification                                 | Drug                                                                                 | Side Effects                                                                                                                                                                                                                                                                                                                          | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|------------------------------------------------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Immunotherapy Agents (Cont.)</b>            |                                                                                      |                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Colony-stimulating factors<br>( <i>Cont.</i> ) | Pegfilgrastim (pegylated granulocyte–colony-stimulating factor, Udenyca®, Neulasta®) | Aortitis<br>Capillary leak syndrome<br>Vasculitis                                                                                                                                                                                                                                                                                     | Aortitis may occur as early as the first week postinitiation.<br>Symptoms of aortitis include fever, abdominal pain, malaise, back pain, and increased inflammatory markers.<br>Assess for signs and symptoms of capillary leak syndrome, including hypotension, hypoalbuminemia, edema, and hemoconcentration, as this presentation may be life threatening.<br>In the presence of capillary leak syndrome, which may be life threatening, discontinue the drug and initiate methylprednisolone.<br>Capillary leak syndrome may require management in the intensive care setting.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021) |
|                                                | Sargramostim (granulocyte macrophage–colony-stimulating factor; Leukine®)            | Capillary leak syndrome (< 1%)<br>Cardiac dysrhythmia<br>Chest pain (15%)<br>Edema (bone marrow transplant: 15%; acute myeloid leukemia: 25%)<br>Hypertension (34%)<br>Hypotension<br>Left bundle branch block (rarely observed)<br>Pericardial effusion (4%–25%)<br>Pericarditis<br>Supraventricular arrhythmia<br>Tachycardia (11%) | Assess for signs and symptoms of capillary leak syndrome, including hypotension, hypoalbuminemia, edema, and hemoconcentration.<br>Establish baseline cardiac status and monitor for acute changes.<br>Use with caution in patients with a history of fluid retention, pulmonary infiltrates, or CHF.<br>Discontinue drug in the presence of arrhythmias.<br>Diuretic therapy may be indicated for fluid retention/edema.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                          |
| Cytokines: interferons                         | Interferon alfa-2b (Intron-A®)                                                       | Cardiac dysrhythmia (< 5%)<br>Cardiomegaly (< 5%)<br>Cardiomyopathy (< 5%)<br>Chest pain (1%–28%, varies by diagnosis)<br>Coronary artery disorder (< 5%)<br>Heart failure (< 5%)<br>Hypotension (< 5%)<br>MI<br>Raynaud disease (< 5%)<br>Supraventricular arrhythmia<br>Tachycardia (< 5%)<br>Vasculitis                            | Monitor closely for signs and symptoms of cardiac complications.<br>Obtain ECGs prior to and during therapy for patients with preexisting cardiac abnormalities and patients in advanced stages of cancer.<br>Discontinue drug in the presence of severe or life-threatening symptoms.<br>Use with caution in patients with a history of cardiovascular disease.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                   |

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**TABLE 16-1.** Cardiotoxicity of Cancer Therapy (*Continued*)

| Classification                                | Drug                                         | Side Effects                                                                                                                                                                                                                                                                                                                                                                 | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|-----------------------------------------------|----------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Immunotherapy Agents (Cont.)</b>           |                                              |                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Cytokines:<br>interferons<br>( <i>Cont.</i> ) | Interferon alfa-2b<br>(pegylated; Sylatron™) | Angina pectoris<br>Bundle branch block (4%)<br>Cardiac dysrhythmia<br>Cardiomyopathy<br>Chest pain (6%–8%)<br>Heart failure<br>Hypotension<br>MI (4%)<br>Pericarditis<br>Supraventricular arrhythmia (4%)<br>Tachycardia<br>Ventricular tachycardia (4%)                                                                                                                     | Assess for a history of cardiovascular disease, including MI or arrhythmic disorder, which is associated with an increased risk for cardiovascular adverse events.<br>Monitor for signs and symptoms of cardiotoxicity.<br>In patients with a history of significant or unstable cardiac disease, do not treat with combination peginterferon and ribavirin.<br>If there is a new onset of ventricular arrhythmia or cardiovascular decompensation, permanently discontinue the drug.<br>Use with caution in patients with a history of cardiac dysfunction.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|                                               | Interferon gamma<br>(Actimmune™)             | Cardiac dysrhythmia<br>Heart failure<br>Hypotension<br>MI<br>Syncope                                                                                                                                                                                                                                                                                                         | Assess for signs and symptoms of cardiac dysrhythmia, including supraventricular tachycardia, atrial flutter, sinus tachycardia, premature ventricular contractions, heart block, and ventricular tachycardia.<br>Monitor for signs and symptoms of cardiotoxicity and adjust dosage or discontinue drug as indicated.<br>Preexisting cardiac conditions, including ischemia, CHF, or arrhythmia, may be exacerbated by flu-like symptoms (e.g., fever, chills) from higher-than-recommended doses.<br>Cardiotoxicity generally is reported in the presence of doses > 100 mcg/m <sup>2</sup> administered 3 times weekly.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Cytokines:<br>interleukins                    | Aldesleukin<br>(interleukin-2; Proleukin™)   | Atrial arrhythmia (grade 4: < 1%)<br>Blood pressure alteration (11%)<br>Bradycardia (< 1%)<br>Capillary leak syndrome<br>Cardiac arrest (1%)<br>Cardiac dysrhythmia (10%)<br>CHF (11%)<br>Coronary artery thrombosis<br>Disorder of cardiovascular system (11%)<br>ECG waveform abnormalities (11%)<br>Edema (15%)<br>Endocarditis (fatal)<br>Hypotension (71%; grade 4: 3%) | Monitor for signs and symptoms of capillary leak syndrome, which may occur immediately following initiation of treatment and is characterized by the following: extravasation of plasma proteins and fluids into the extravascular space, severe hypotension, cardiac arrhythmias, angina, MI, respiratory insufficiency requiring intubation, gastrointestinal bleeding or infarction, renal insufficiency, edema, and mental status changes.<br>Capillary leak syndrome–associated hypotension is characterized by a drop in mean arterial blood pressure within 2–12 hours; reduced organ perfusion may result in death.<br>Assess for hypovolemia by catheterization and central pressure monitoring.<br>Monitor serum electrolytes at baseline and daily during treatment.<br>Monitor vital signs (e.g., temperature, pulse, blood pressure, respiration rate), weight, and fluid intake and output daily.<br>Discontinue treatment in the event of reduced organ perfusion, including altered mental status, decreased urine output, and systolic blood pressure < 90 mm Hg.<br>Administer IV fluids with careful monitoring of fluid status. Initiate dopamine (1–5 mcg/kg/min) prior to the onset of hypotension; phenylephrine hydrochloride (1–5 mcg/kg/min) has also been used to stabilize blood pressure.<br>Withhold interleukin-2 in patients developing ventricular dysrhythmias until cardiac ischemia and wall motion can be assessed. |

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**TABLE 16-1.** Cardiotoxicity of Cancer Therapy (*Continued*)

| Classification                                 | Drug                                                                    | Side Effects                                                                                                                                                                                                                                                                                           | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|------------------------------------------------|-------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Immunotherapy Agents (Cont.)</b>            |                                                                         |                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Cytokines:<br>interleukins<br>( <i>Cont.</i> ) | Aldesleukin<br>(interleukin-2;<br>Proleukin®)<br>( <i>Cont.</i> )       | MI (1%)<br>Myocardial ischemia (grade 4: 1%)<br>Myocarditis<br>Peripheral edema (28%)<br>Second-degree atrioventricular block (< 1%)<br>Supraventricular tachycardia (12%; grade 4: 1%)<br>Tachycardia (23%)<br>Vasodilation (13%)<br>Ventricular premature beats (1%)<br>Ventricular tachycardia (1%) | If adverse events occur, the drug should be withheld and not dose reduced.<br>Most adverse reactions are self-limiting and usually, but not invariably, reverse or improve within 2–3 days of discontinuing therapy.<br>Electrical changes caused by cytokine immunotherapy usually relate to cellular swelling or inflammatory cytokine release disrupting conduction pathways. Capillary permeability and hypovolemia enhance the risk of supraventricular tachycardia.<br>Electrical changes associated with immunotherapy agents generally necessitate temporary discontinuation of the drug. Once inflammatory effects have been resolved, rechallenge is possible.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)     |
|                                                | Oprelvekin<br>(interleukin-11;<br>Neumega®)                             | Cardiomegaly (21%)<br>Edema (59%)<br>Increased plasma volume<br>Palpitations (14%)<br>Syncope (13%)<br>Tachyarrhythmia (20%)<br>Ventricular arrhythmia                                                                                                                                                 | Monitor for signs and symptoms of cardiotoxicity and adjust dosage or discontinue drug as indicated.<br>Monitor heart rate, blood pressure, and ECG.<br>Use with caution in patients with a history of atrial arrhythmias, thromboembolic disorders, and left ventricular dysfunction or CHF.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                                                                                                |
| Monoclonal antibodies:<br>chimeric             | Cetuximab<br>(anti-epidermal growth factor receptor antibody; Erbitux®) | Cardiorespiratory event (2%–3%)<br>Sudden cardiac death (2%–3%)                                                                                                                                                                                                                                        | Monitor electrolytes, particularly magnesium, calcium, and potassium levels, throughout treatment and up to 8 weeks after the conclusion of therapy, and maintain within normal limits.<br>Monitor for infusion reaction up to 1 hour after infusion; in the presence of reaction, monitor until the reaction is resolved.<br>Concomitant use of this drug with radiation (and cisplatin) increases the risk of life-threatening events, including cardiac events and electrolyte abnormalities.<br>MI has been observed in patients receiving cetuximab for head and neck cancer but was not evident in patients receiving the drug for metastatic colorectal cancer.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)       |
|                                                | Dinutuximab<br>(anti-GD2 antibody; Unituxin®)                           | Capillary leak syndrome (40%), including fatal cases<br>Edema (17%)<br>Hypertension (14%)<br>Hypotension (60%)<br>Tachycardia (19%)                                                                                                                                                                    | Monitor blood pressure during infusion.<br>In moderate to severe cases, hold the drug until supportive management resolves capillary leak syndrome, after which the drug may be restarted at a reduced rate.<br>In life-threatening cases, withhold the drug until the next cycle or permanently discontinue if capillary leak syndrome recurs or persists.<br>In the presence of symptomatic hypotension (systolic blood pressure < LLN for age or decreased by > 15% from baseline), stop therapy and implement supportive management. The infusion may be reinstated at a reduced rate 2 hours after symptoms resolve.<br>Administer IV hydration prior to each infusion.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021) |

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**TABLE 16-1.** Cardiotoxicity of Cancer Therapy (*Continued*)

| Classification                                   | Drug                                                                                            | Side Effects                                                                                                                                                                              | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|--------------------------------------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Immunotherapy Agents (Cont.)</b>              |                                                                                                 |                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Monoclonal antibodies: chimeric ( <i>Cont.</i> ) | Rituximab (anti-CD20 antibody; Rituxan <sup>®</sup> )                                           | Cardiac complications (29%)<br>Heart failure<br>Hypertension (6%–12%)<br>Hypotension (10%)<br>Peripheral edema (8%–16%)<br>Supraventricular arrhythmia (4.5%)<br>Vasculitis               | Monitor older patients for signs and symptoms of cardiac complications, including supraventricular arrhythmias, for whom these events are more common.<br>Monitor for changes in blood pressure; however, hypertension has primarily been reported in patients with rheumatoid arthritis who are being treated with this agent.<br>Monitor patients with a history of arrhythmia and angina for new-onset or exacerbated arrhythmia.<br>Monitor patients with a history of cardiac abnormalities or cardiac reactions for infusion reaction, as risk is increased.<br>Assess for inflammatory skin lesions, which may appear on the abdomen and lower extremities and become purpuric, as these have been observed in the presence of vasculitis in patients treated for B-cell chronic lymphoid leukemia.<br>Monitor for hypotension, which may be a sign of infusion reaction and is most commonly observed during the first infusion or in patients with active or a history of cardiac or pulmonary conditions or adverse events.<br>Perform cardiac monitoring during infusion for patients with a cardiac history of arrhythmia or angina or in those who develop significant arrhythmia during treatment.<br>Discontinue drug in the presence of life-threatening cardiac arrhythmias.<br>After symptoms resolve, resume treatment by reducing the infusion rate by 50%.<br>The risk of potentially fatal cardiac arrhythmia is increased in patients with current arrhythmia or history of arrhythmia and angina.<br>Infusion-related deaths have occurred within 24 hours of infusion.<br>Infusion-related complications include MI, ventricular fibrillation, and cardiogenic shock. (Biogen & Genentech, 2016; Truven Health Analytics, 2021; Wolters Kluwer Health, 2021) |
| Monoclonal antibodies: human                     | Ado-trastuzumab emtansine (anti-HER2 antibody conjugated with emtansine; Kadcyla <sup>®</sup> ) | Hypertension (5.1%)<br>Left ventricular cardiac dysfunction (1.8%)<br>Pulmonary arterial hypertension                                                                                     | Evaluate LVEF prior to treatment initiation and at regular intervals (e.g., every 3 months) during treatment and within 3 weeks if LVEF is $\leq$ 45%.<br>The drug has a black box warning that reduction of LVEF may occur; assess LVEF before, during, and after treatment. The drug may need to be held or discontinued if LVEF does not resolve. (Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                                                  | Elotuzumab (anti-SLAMF7 antibody; Empliciti <sup>™</sup> )                                      | Bradycardia (66%)<br>Decreased systolic arterial pressure (28.9%)<br>Increased diastolic arterial pressure (17.3%)<br>Increased systolic arterial pressure (33.3%)<br>Tachycardia (47.8%) | Monitor for signs and symptoms of cardiotoxicity, and manage symptoms as indicated.<br>Monitor vital signs for changes in blood pressure (increase or decrease).<br>Assess for cardiac abnormalities, particularly in patients receiving combination therapy with lenalidomide and dexamethasone, with which their presentations have been observed. (Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

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**TABLE 16-1.** Cardiotoxicity of Cancer Therapy (*Continued*)

| Classification                                | Drug                                                                                | Side Effects                                                                                                                                                                                                             | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|-----------------------------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Immunotherapy Agents (Cont.)</b>           |                                                                                     |                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Monoclonal antibodies: human ( <i>Cont.</i> ) | Ramucirumab (anti-vascular endothelial growth factor receptor 2 antibody; Cyramza®) | Arterial thromboembolism (2%)<br>Hypertension (11%–36%)<br>Hypertension (grade 3 or higher: 3% in monotherapy; 6%–15% in combination therapy)<br>Peripheral edema (16%–25% in combination therapy)                       | Monitor blood pressure every 2 weeks or more frequently during therapy.<br>Control hypertension before treatment initiation.<br>Pause treatment until severe hypertension is controlled.<br>Permanently discontinue therapy for hypertension uncontrolled by antihypertensives, hypertensive crisis, or hypertensive encephalopathy.<br>Serious and fatal arterial thrombotic events may occur with this therapy.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Monoclonal antibodies: humanized              | Alemtuzumab (anti-CD52 antibody; Campath®)                                          | Atrial fibrillation<br>Cardiomyopathy<br>Chest discomfort (7%)<br>CHF<br>Decreased cardiac ejection fraction<br>Peripheral edema (5%)<br>Tachycardia (8%)                                                                | Monitor vital signs before and during infusions.<br>Monitor for infusion reactions during and for a minimum of 2 hours after each infusion, with additional monitoring as indicated for patients with conditions that have a higher risk of cardiovascular or pulmonary complications.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|                                               | Bevacizumab (anti-vascular endothelial growth factor antibody; Avastin®)            | Hypertension (19%–42%; grade 3–5: 5%–18%)<br>CHF (1.6%–4%)<br>Hypertensive encephalopathy<br>Hypotension (7%–15%)<br>Ischemic heart disease (1%)<br>Left ventricular cardiac dysfunction (10%)<br>Peripheral edema (15%) | Monitor for severe hypertension (grade 3–4), for which holding or stopping the drug may be necessary.<br>Monitor for mild or moderate blood pressure elevations, which also may be a sign of infusion reaction or posterior reversible encephalopathy syndrome.<br>Monitor for left ventricular dysfunction and CHF for up to 6 months following therapy.<br>Monitor for hypertensive crisis, particularly in patients with metastatic renal cell carcinoma receiving combination therapy with interferon alfa.<br>Continue to monitor blood pressure even after discontinuation of bevacizumab in patients with hypertension.<br>Check baseline vital signs, particularly blood pressure, with each clinic visit or at least every 2–3 weeks during therapy, with routine monitoring after treatment.<br>Discontinue therapy in the presence of CHF.<br>Initiate antihypertensive therapy with elevated blood pressure, as this has been demonstrated to control treatment-related elevations in blood pressure in most cases.<br>Hold treatment in the presence of uncontrolled hypertension, and discontinue in the presence of hypertensive crisis or encephalopathy.<br>Temporarily suspend treatment if urine shows 3+ urine dipstick reading, particularly if accompanied by hypertension; perform 24-hour urine collection and analysis in patients with a dipstick reading of 2+.<br>Risk of severe hypertension or hypotension is increased in patients aged 65 and older with metastatic colorectal cancer.<br>Hypertension may persist for several weeks after discontinuation of bevacizumab.<br>CHF occurs more frequently in patients who have received prior anthracyclines or left chest wall irradiation.<br>(Truven Health Analytics, 2021; Wolters Kluwer Health, 2021) |

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**TABLE 16-1.** Cardiotoxicity of Cancer Therapy (*Continued*)

| Classification                                    | Drug                                                      | Side Effects                                                                                                                                                                      | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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| <b>Immunotherapy Agents (Cont.)</b>               |                                                           |                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Monoclonal antibodies: humanized ( <i>Cont.</i> ) | Pertuzumab (anti-HER2 antibody; Perjeta®)                 | CHF (0.9%–4%)<br>Left ventricular dysfunction (3%–7%)                                                                                                                             | Assess LVEF prior to initiation of pertuzumab and at regular intervals (e.g., every 3 months) during therapy to ensure that ventricular function is not impaired.<br>Monitor for hypersensitivity reactions for 60 minutes after the first infusion and 30 minutes after subsequent infusions.<br>Withhold pertuzumab if a significant decrease in LVEF occurs. Reassess within 3 weeks. If it continues to be decreased, discontinue pertuzumab.<br>LVEF and CHF have been reported and may require a pause in therapy or discontinuation; cardiotoxicity risk increases with prior anthracycline therapy or chest wall irradiation. (Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                                                   | Pertuzumab, trastuzumab, and hyaluronidase-zzxf (Phesgo®) | Arrhythmias<br>Cardiomyopathy (0.8%–1.2%)<br>Hypertension                                                                                                                         | Perform a thorough cardiac history prior to initiation of therapy.<br>Assess LVEF prior to initiation and at regular intervals during treatment.<br>The dose should be withheld for at least 3 weeks based on specific LVEF parameters outlined in the package insert.<br>Treatment can be resumed after 3 weeks based on improvements in follow-up LVEF testing, as outlined in the package insert.<br>Treatment should be permanently discontinued if there is no improvement in the LVEF after 3 weeks or the patient is symptomatic.<br>Assess LVEF every six months for two years upon completion of treatment. (Genentech, 2020)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|                                                   | Trastuzumab (anti-HER2 antibody; Herceptin®)              | Cardiac dysrhythmia (3%)<br>Edema (4.7%)<br>Heart failure (0.4%–3.2% with adjuvant therapy; 7%–28% in metastatic breast cancer)<br>Palpitations (3%)<br>Peripheral edema (5%–22%) | Perform an assessment, including cardiac history, physical examination, and LVEF evaluation by MUGA scan or echo at baseline immediately prior to therapy, every 3 months during treatment, every 6 months following treatment, and every 4 weeks if the drug is held for significant LVEF dysfunction.<br>Frequently monitor for deteriorating cardiac function.<br>Assess for asymptomatic decreases in LVEF and symptomatic myocardial dysfunction, arrhythmias, hypertension, disabling cardiac failure, and cardiomyopathy, which have been observed during treatment.<br>LVEF monitoring is critical for patients with the following risks for CHF: <ul style="list-style-type: none"> <li>• Baseline LVEF &lt; 54%</li> <li>• Age &gt; 50 years</li> <li>• Receiving antihypertensive treatment</li> <li>• Body mass index &gt; 25 kg/m<sup>2</sup></li> </ul> Evaluate LVEF before, during, and for at least 2 years after treatment.<br>Decreases in LVEF may necessitate holding or discontinuing treatment.<br>Cardiotoxicity contributed to treatment discontinuation in 2.6%–15% of patients receiving adjuvant therapy with IV trastuzumab.<br>Cardiac dysfunction risk is increased in patients receiving anthracycline-based therapy during or after treatment with trastuzumab.<br>Advanced age may increase the probability of cardiac dysfunction.<br>Cardiotoxicity risk is increased in older patients with breast cancer.<br>Treatment has been associated with cardiac death. |

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**TABLE 16-1.** Cardiotoxicity of Cancer Therapy (*Continued*)

| Classification                                    | Drug                                                          | Side Effects                                                                                                                                                                                                                                                        | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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| <b>Immunotherapy Agents (<i>Cont.</i>)</b>        |                                                               |                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Monoclonal antibodies: humanized ( <i>Cont.</i> ) | Trastuzumab (anti-HER2 antibody; Herceptin®) ( <i>Cont.</i> ) |                                                                                                                                                                                                                                                                     | Symptomatic myocardial dysfunction increases 4–6-fold with monotherapy or combination therapy compared to treatment without trastuzumab.<br>Hold anthracycline-based treatment for at least 7 months after discontinuation of trastuzumab. (Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Monoclonal antibodies: murine                     | Blinatumomab (anti-CD19/CD3 antibody; Blincyto®)              | Cardiac dysrhythmia, including atrial fibrillation, atrial flutter, bradycardia, sinus bradycardia, sinus tachycardia, supraventricular tachycardia, and tachycardia (14%)<br>Edema (18%)                                                                           | Monitor for signs and symptoms of cardiotoxicity, including capillary leak syndrome, which may result from cytokine release syndrome. (Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Miscellaneous: autologous cellular immunotherapy  | Sipuleucel-T (Provenge®)                                      | Hypertension (8%)                                                                                                                                                                                                                                                   | Monitor for signs and symptoms of hypertension, and manage as indicated.<br>Observe patients for at least 30 minutes after each infusion for acute infusion reactions, especially those with cardiac or pulmonary conditions.<br>Deep venous thrombosis and pulmonary embolism have occurred, usually in patients with risk factors for these conditions.<br>Cerebrovascular events, such as stroke, and MI have also occurred. (Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Miscellaneous: immunomodulators                   | Lenalidomide (Revlimid®)                                      | Atrial fibrillation (grade 3–4: 3.7%)<br>Cerebrovascular accident (1.4%–2.3%)<br>CHF (grade 3–4: 1.4%)<br>Edema (10.1%)<br>Heart failure (1%–10%)<br>Hypotension (7.1%)<br>MI (< 5%)<br>Peripheral edema (20.3%–26.3%)<br>Syncope (1.4%–2.8%)<br>Tachycardia (1.7%) | Establish baseline blood pressure, heart rate and regularity, and ECG findings to identify drug-related changes.<br>Monitor heart rate, rhythm, and blood pressure frequently during therapy or with new cardiac symptoms. Assess for atrial fibrillation and CHF, which may be fatal in patients receiving lenalidomide in combination with dexamethasone, as observed in patients treated for multiple myeloma.<br>Assess for cerebrovascular accident and MI in patients with multiple myeloma who have an increased risk of stroke while being treated with lenalidomide; risk factors for thrombosis include use of erythropoiesis-stimulating agents and estrogen agents.<br>Assess for thrombosis, which may occur at least 2.7 months after treatment, particularly in patients who have not undergone prophylaxis.<br>Assess for hypotension, edema, syncope, and tachycardia, which have been observed in patients treated in combination with dexamethasone.<br>Thromboprophylaxis is recommended during treatment, especially for those at elevated risk for stroke; patients should be assessed and managed for risk factors for stroke, including hyperlipidemia, hypertension, and smoking.<br>Cardiac failure was observed in patients treated for chronic lymphocytic leukemia. (Truven Health Analytics, 2021; Wolters Kluwer Health, 2021) |

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**TABLE 16-1.** Cardiotoxicity of Cancer Therapy (*Continued*)

| Classification                                   | Drug                          | Side Effects                                                                                                                                                                                                                                                     | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|--------------------------------------------------|-------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Immunotherapy Agents (Cont.)</b>              |                               |                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Miscellaneous: immunomodulators ( <i>Cont.</i> ) | Pomalidomide (Pomalyst®)      | Acute MI (undefined)<br>Arterial thromboembolism (undefined)<br>Atrial fibrillation (undefined)<br>Cerebrovascular accident (undefined)<br>Peripheral edema (25%)                                                                                                | Venous and arterial thromboembolic events have been seen in patients with multiple myeloma. Thromboprophylaxis is recommended. (Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|                                                  | Thalidomide (Thalomid®)       | Atrial fibrillation (grade 3–4: 5%)<br>Bradyarrhythmia (3%)<br>Cardiac dysrhythmia<br>Edema (13%–56%; grade 3: 6%)<br>Heart failure<br>Hypotension (3%)<br>Ischemic heart disease (11.1%)<br>MI (1.3%)<br>Orthostatic hypotension (3%)<br>Peripheral edema (34%) | Assess for ischemic heart disease, MI, and stroke.<br>Assess for bradycardia, particularly in patients taking drugs that may reduce heart rate and at an increased risk for this toxicity.<br>Monitor for hypotensive reaction, including dizziness or orthostatic hypotension.<br>Monitor for signs and symptoms of thromboembolism, including upper and lower extremity swelling, shortness of breath, or chest pain.<br>Assess patients for dizziness, palpitations, or other symptoms of dysrhythmias.<br>Assess for cardiac arrhythmias, including ECG abnormalities, atrial fibrillation, bradycardia, tachycardia, sick sinus syndrome, and MI.<br>Treatment may need to be held or discontinued in the presence of bradycardia.<br>Initiate thromboprophylaxis when not contraindicated.<br>Evaluate for drugs that increase the risk of thromboembolism.<br>Cardiotoxicity often is observed in combination with dexamethasone.<br>Bradyarrhythmia and hypotension may result from activation of the vasovagal pathway. (Truven Health Analytics, 2021; Wolters Kluwer Health, 2021) |
| <b>Hormone Therapy Agents</b>                    |                               |                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Androgen inhibitor                               | Abiraterone acetate (Zytiga®) | Cardiac dysrhythmia (7.2%)<br>Cardiorespiratory arrest (0.5%)<br>Chest discomfort/pain (3.8%; grade 3–4: 0.5%)<br>Edema (25.1%–26.7%)<br>Heart failure (2.3%–2.6%)<br>Hypertension (8.5%–37%)<br>MI (rare, but may be fatal)<br>Torsades de pointes              | Monitor blood pressure and fluid balance/retention at least monthly during therapy.<br>Monitor serum potassium monthly.<br>Use with caution in patients who are sensitive to increased blood pressure, hypokalemia, or fluid retention. Corticosteroids may be coadministered to reduce the incidence and severity of edema.<br>Use with caution in patients with known heart or vascular disease known to be compromised by hypertension, hypokalemia, or fluid retention.<br>Heart failure may lead to treatment discontinuation. (Truven Health Analytics, 2021; Wolters Kluwer Health, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

bpm—beats per minute; CHF—congestive heart failure; CYP—cytochrome P450; ECG—electrocardiogram; echo—echocardiography; HER2—human epidermal growth factor receptor 2; IV—intravenous; LLN—lower limit of normal; LVEF—left ventricular ejection fraction; MI—myocardial infarction; ms—milliseconds; MUGA—multigated acquisition; QTc—corrected QT interval; QTcF—corrected QT interval using Fridericia's calculation

## c) Incidence

- (1) Atrial fibrillation is the most common supraventricular dysrhythmia in patients with cancer and may occur acutely, during or after chemotherapy and radiation therapy, or following surgical intervention.
- (2) Atrial fibrillation most notably occurs in the postoperative setting, with 13%–20% following lung resection and 20%–25% following esophageal surgery (Chu et al., 2019; Ganatra et al., 2018; Tang, 2019).

## d) Risk factors (Chu et al., 2019; Ganatra et al., 2018)

- (1) Older age
- (2) Preexisting cardiovascular disease
- (3) Hypertension
- (4) Heart failure
- (5) Sleep apnea
- (6) Pericardial disease
- (7) Pulmonary embolism
- (8) Valvular disease
- (9) Chronic obstructive pulmonary disease
- (10) Electrolyte abnormalities
- (11) Thyroid disorders
- (12) Chronic kidney disease

## e) Clinical manifestations (Chu et al., 2019)

- (1) Palpitations
- (2) Chest discomfort
- (3) Dyspnea and fatigue may result from decreased cardiac output due to loss of atrial kick (approximately one-third of cardiac output), which worsens all other cardiac disease symptoms.
- (4) Dizziness

## f) Assessment

- (1) Assess patient history for known medical conditions or medications that may precipitate dysrhythmias. Elimination of preventable risks may reduce incidence or severity (López-Fernández et al., 2019).
- (2) Obtain a baseline electrocardiogram (ECG).
- (3) Maintain ongoing monitoring (continuous or intermittent) of ECG rhythm.
- (4) Compare apical and peripheral heart rates (Asnani et al., 2017).
- (5) Perform follow-up assessments of vital signs and for symptoms of dyspnea, hypoxemia (shown as low oxygen saturation), hypotension, or chest discomfort (Asnani et al., 2017).
- (6) Replace electrolytes and maintain within normal ranges.

## g) Collaborative management

- (1) Correct contributing factors, such as hypoxemia, anemia, fluid imbalance, and electrolyte abnormalities.
- (2) Administer electrolyte replacement to a goal potassium value greater than 4 mEq/L and magnesium value greater than 2 mEq/L (Abu Rmilah et al., 2020).
- (3) Optimal calcium levels are not established, but the usual goal is ionized calcium levels greater than 1.1 mEq/L.

## h) Patient and family education

- (1) Patients with truly lone atrial fibrillation need to be aware that their risk of stroke is extremely low, approximately 1.3% over a 15-year period (Lane et al., 2015). However, regular clinical reassessment of their stroke risk using the CHA2DS2-VASc score is essential, particularly as age increases and the prospect of developing comorbidities becomes more likely (Lane et al., 2015).
- (2) All patients with atrial fibrillation should be aware of the risk factors that can increase their risk of stroke.
- (3) Patients need to be aware of the potential harms of medications used to treat atrial fibrillation (e.g., beta-blockers, antidysrhythmics), which can include life-threatening ventricular arrhythmias (and lead to death in rare cases), deterioration of left ventricular systolic function, and organ toxicity (particularly with long-term use).
- (4) Patients need to be aware that late recurrences of atrial fibrillation after cardioversion or catheter ablation are a possibility and that more than one procedure may be required.
- (5) Patients need to know what has caused their atrial fibrillation, how it will affect their lives (consequences), and the therapeutic options.
- (6) To enable realistic treatment expectations, patients need to know what they have been prescribed and, why they are taking it, how to take it (e.g., dose; frequency; timings; with, before, or after food; with other tablets), what will happen if they fail to adhere as prescribed, any factors that may modify drug efficacy, any possible side effects, and the likelihood of treatment success or failure (Lane et al., 2015).

## 4. QT prolongation

## a) Definition

- (1) QT prolongation is an abnormality in the conduction system of the heart that

can put patients at risk for ventricular arrhythmias (i.e., torsades de pointes, syncope, and sudden death) (Vandael et al., 2017).

- (2) The QT interval represents the duration of electrical depolarization and repolarization of the ventricles, beginning at the initiation of the QRS complex and ending where the T wave returns to the isoelectric baseline (Abu Rmilah et al., 2020).
- (3) The approximate duration of a regular QT interval is 350–460 ms.
- (4) The QT interval is inversely correlated with heart rate; therefore, it is shorter with more rapid heart rates and longer with slower rates.
- (5) Because of this inverse relationship, the QT interval is routinely transformed (normalized) using various formulas into a heart rate–dependent corrected value known as the QTc interval.
- (6) The QTc interval represents the QT interval at a standardized heart rate of 60 beats per minute.
  - (a) Several correction formulas have been developed to improve the accuracy of QT measurement with QTc values (Fridericia, 2003; Kim, Masha, et al., 2021).
  - (b) QTc intervals at the upper limit of normal have been proposed for males (greater than 450 ms) and females (greater than 460 ms).
  - (c) A QTc greater than 500 ms or a QT change from a baseline of greater than 60 ms should be of particular concern because it can predispose patients to torsades de pointes (Herrmann, 2020). This polymorphic ventricular tachyarrhythmia appears on ECG as a continuous twisting of the vector of the QRS complex around the isoelectric baseline.
  - (d) Torsades de pointes may degenerate into ventricular fibrillation, leading to sudden cardiac death (Abu Rmilah et al., 2020).
  - (e) A feature of torsades de pointes is the pronounced prolongation of the QT interval in the supraventricular beat preceding the arrhythmia.

#### b) Pathophysiology

- (1) The arrhythmogenic mechanisms underlying QT prolongation in patients with cancer are not well established.

- (2) Prolonged QT interval may be caused by the tumor, cancer treatment, metabolic abnormalities (e.g., abnormal electrolytes), or underlying cardiac disease (e.g., myocardial ischemia, heart failure), which create an arrhythmogenic substrate (Tamargo et al., 2015).
- (3) The most commonly identified antineoplastic agents that affect cardiac repolarization include histone deacetylase inhibitors, tyrosine kinase inhibitors (TKIs), the BRAF inhibitor vemurafenib, and arsenic trioxide (Moslehi & Deininger, 2015; Nair et al., 2017).

#### c) Incidence

- (1) Variability exists in the incidence of QTc prolongation in various cancer drugs, ranging from 0% to 22.7%. Severe prolongation (QTc greater than 500 ms) has been reported in 0%–5.2% (Porta-Sanchez et al., 2017; Wolters Kluwer Health, 2021).
- (2) However, the reported incidence of QTc prolongation is higher with specific TKIs, such as nilotinib (38.7%) and dasatinib (41.7%) (Abu Rmilah et al., 2020).

#### d) Risk factors

- (1) Medications known to prolong QTc, including arsenic trioxide, dasatinib, 5-fluorouracil, lapatinib, nilotinib, pazopanib, sunitinib, tamoxifen, temsirolimus, and vorinostat (Kim, Masha, et al., 2021)
- (2) Presence of multiple comorbidities (e.g., preexisting cardiac disease)
- (3) Polypharmacy with concomitant QT-prolonging agents (e.g., antiemetics, antidepressants, antibiotics)
- (4) Electrolyte disturbances (particularly hypokalemia and hypomagnesemia) and other metabolic abnormalities
- (5) Diurnal effects
- (6) Autonomic tone

#### e) Clinical manifestations (Kim, Irizarry-Caro, et al., 2021)

- (1) Palpitations
- (2) Syncope
- (3) Presyncope

#### f) Assessment

- (1) Identify the etiology of the QT prolongation, such as toxic substances, other metabolic abnormalities, or primary or structural abnormalities of the heart itself.
- (2) Replace electrolytes (potassium and magnesium), and maintain within normal ranges.

#### g) Collaborative management

- (1) Correct contributing factors, such as hypoxemia, anemia, fluid imbalance, and electrolyte abnormalities.
- (2) Administer electrolyte replacement to a goal potassium value greater than 4 mEq/L and magnesium value greater than 2 mEq/L (Kim, Irizarry-Caro, et al., 2021).
  - (a) Optimal calcium levels are not established, but ionized calcium levels below 2.8 mg/dl are a reasonable threshold to begin calcium replacement therapy.
  - (b) Patients with hypotension or low cardiac output may require calcium replacement when ionized calcium falls below 3.2–3.6 mg/dl.
  - (c) Replacement therapy should be monitored with ionized calcium levels (Kim, Irizarry-Caro, et al., 2021; Kim, Masha, et al., 2021).
- (3) Prior to starting medications with the potential for QT prolongation, obtain a baseline ECG with QT measurement, with subsequent ECG monitoring for QT intervals as indicated by prescribing information.
- (4) In patients with excessive corrected QT interval prolongation (greater than 500 ms), QT-prolonging cancer drugs should not be initiated, and potential causes or contributing factors should be evaluated and corrected.
- (5) Concomitant treatment with QT-prolonging drugs (e.g., antiarrhythmics, antibiotics, antifungals) should be avoided.

#### h) Patient and family education

- (1) Teach patients and families the symptoms of QT prolongation and the potential urgency of treatment.
- (2) Once QT prolongation has been identified, teach preventive strategies, such as hydration or electrolyte replacement. Emphasize that vomiting or diarrhea may disrupt fluid or electrolyte balance.
- (3) Patients need to be aware of the medications that can cause QT prolongation.

### C. Vascular abnormalities: hypertension

1. Definition: Hypertension is a systolic blood pressure of 140 mm Hg or greater or a diastolic blood pressure of 90 mm Hg or greater (Unger et al., 2020).
  - a) Hypertension is the most frequent comorbid condition reported in patients with cancer and is associated with an increased risk of cardiovas-

cular complications, including stroke, myocardial infarction, and heart failure (de Souza et al., 2015; Unger et al., 2020).

- b) It is particularly increased in patients treated with angiogenesis inhibitors, commonly known as vascular signaling pathway (VSP) inhibitors, including the VEGF inhibitors and other small molecule TKIs (Lankhorst et al., 2015; Nair et al., 2017; Tini et al., 2019). Drug-related hypertension can occur from initiation until one year after treatment onset (Zamorano et al., 2016).
- ### 2. Pathophysiology
- a) The exact mechanism underlying the development of hypertension related to cancer therapy is unknown. Proposed mechanisms include abnormalities in endothelial function and angiogenesis, nitric oxide pathway inhibition, decrease in vascular wall compliance and flexibility, oxidative stress, and glomerular injury developing from loss of VEGF effect, as well as renal thrombotic microangiopathy (Katsi et al., 2019; Priori et al., 2015; Zamorano et al., 2016).
  - b) Multikinase inhibition results in antiangiogenesis by blocking the BCR-ABL receptor and the actions of VEGF, which decreases cellular nitric oxide (Jiang et al., 2021). Hypertension is related to the loss of the VEGF effect on the vascular endothelial wall leading to diminished nitric oxide synthase and loss of the vasodilatory effects of nitric oxide (de Souza et al., 2015; Plummer et al., 2019).
  - c) Lower nitric oxide levels are associated with sodium and water retention (Rust & Ekmekcioglu, 2017).
  - d) Vasoconstriction results from the interference with nitric oxide production in the arteriolar walls by the VSP inhibitors (Agarwal et al., 2018).
- ### 3. Incidence
- a) Hypertension incidence has increased to 80% in patients with cancer treated with VEGF inhibitors (Lankhorst et al., 2015; Tini et al., 2019).
  - b) Hypertension associated with antiangiogenic therapies and multikinase inhibitors occurs with high frequency (4%–80%) and is dose dependent (Agarwal et al., 2018). Approximately 11%–16% of patients receiving bevacizumab have significant hypertension that requires adding or adjusting antihypertensive medications (Tini et al., 2019).
- ### 4. Risk factors
- a) Advancing age
  - b) Preexisting hypertension or cardiovascular disease (Katsi et al., 2019)
  - c) Treatment with bevacizumab, pazopanib, sorafenib, sunitinib, or vandetanib (Katsi et al., 2019)

- d) Proteinuria usually precedes hypertension with bevacizumab therapy (Dempsey et al., 2021).
  - e) Renal insufficiency, hyperthyroidism, Cushing syndrome, increased intracranial pressure, and hypomagnesemia independent of chemotherapy toxicity (Dempsey et al., 2021)
  - f) Medications such as antidepressants, including tricyclic antidepressants and selective serotonin reuptake inhibitors
  - g) Race: Hypertension tends to be more common, more severe, occurs earlier in life, and is associated with more significant target-organ damage in Black people.
5. Clinical manifestations
- a) Most patients with high blood pressure have no signs or symptoms, even if blood pressure readings reach dangerously high levels.
  - b) A few people with high blood pressure may have headaches, shortness of breath, or nosebleeds, but these signs and symptoms are not specific and usually do not occur until blood pressure has reached a severe or life-threatening stage.
  - c) Increases in blood pressure with multikinase inhibitors and antiangiogenic agents may be asymptomatic or accompanied by headache, visual disturbances, fatigue, tachycardia, or heart failure.
6. Assessment (Unger et al., 2020)
- a) Obtain a comprehensive patient history to establish a baseline. Assess for medications (e.g., sinus or cold remedies) or clinical conditions that may contribute to altered blood pressure.
  - b) Evaluate laboratory values to determine specific cardiovascular risk factors prior to starting VSP inhibitors.
  - c) Blood pressure assessment should have a minimum of two standardized measurements and set a goal of less than 140/90 mm Hg for most patients, following recommendations for all adults.
  - d) Higher-risk patients, including those with diabetes or chronic kidney disease, should achieve a lower goal (e.g., 130/80 mm Hg).
  - e) Evaluate pain control, as pain may contribute to hypertension.
  - f) Assess for stress management and other medications used in these patients (e.g., steroids, nonsteroidal anti-inflammatory drugs, erythropoietin) that can cause hypertension to estimate blood pressure adequately.
7. Collaborative management of hypertension (Plummer et al., 2019; Unger et al., 2020)
- a) Early diagnosis and control of blood pressure to the recommended guideline parameters allow for effective antiangiogenic therapy for optimal cancer treatment (Agarwal et al., 2018).
  - b) A baseline blood pressure measurement and regular monitoring are recommended while patients are receiving VEGF inhibitors, especially during the first cycle of chemotherapy, when most patients experience an elevation in blood pressure.
  - c) Blood pressure should be actively monitored weekly during the first cycle of VSP inhibitor therapy and then at least every two to three weeks for the duration of treatment.
  - d) Patients with preexisting hypertension and on multiple antihypertensive agents should be evaluated for renal function and proteinuria.
  - e) Antihypertensive therapy must be individualized to patients according to medical history and the specific properties of different antihypertensive agents (Whelton et al., 2018; Williams et al., 2018).
  - f) Antihypertensive agent classes that have been specifically prescribed to control hypertension associated with VSP inhibitor therapy include thiazide diuretics, beta-blockers, dihydropyridine calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers (Agarwal et al., 2018; Whelton et al., 2018). Some agents may be preferable (e.g., renin-angiotensin or sympathetic system inhibitors) over others (e.g., thiazide diuretics) to minimize the risk of electrolyte depletion.
  - g) Hypertension associated with TKIs is typically manageable with appropriate therapy. Early intervention is key to minimizing additional cardiovascular adverse effects such as heart failure (Agarwal et al., 2018).
  - h) Patients should keep a blood pressure measurement log, especially during the first week of treatment, because the magnitude of elevation is unpredictable.
  - i) Target blood pressure should be based on the *2020 International Society of Hypertension Global Hypertension Practice Guidelines* (Unger et al., 2020).
  - j) Antihypertensive therapy should be adjusted accordingly based on associated comorbidities (e.g., less than 140/90 mm Hg) in patients with diabetes or chronic kidney disease.
8. Patient and family education
- a) Hypertension can be life threatening and cause stroke. Patients should be prepared to recognize signs of a hypertensive crisis or stroke.
    - (1) Memory lapses
    - (2) Blackouts or near syncope
    - (3) Visual abnormalities
    - (4) Persistent headache



- (5) Slurred words
- (6) Numbness or tingling of an extremity
- (7) Facial droop
- b) Patients may require guidance with self-administration of antihypertensive agents.
- c) Many antihypertensive agents can cause immediate orthostasis, dizziness, nausea, and risk of falling.
- d) Patients should be instructed to use a validated, automated oscillometric device that measures blood pressure in the brachial artery (upper arm) and perform measurements in a quiet room after five minutes of rest in the seated position with the back and arm supported.
- e) Blood pressure generally should be checked in both arms to determine if a difference exists. It is important to use an appropriately sized arm cuff.
- f) Adherence to taking medications as prescribed should be emphasized to patients.
- g) Patients should be aware of the potential side effects of medications and when to report them to their healthcare provider.
- h) Before starting TKIs, patients need to have a baseline blood pressure measurement and be aware of the target blood pressure.

#### D. Venous thromboembolism (VTE)

1. Definition: VTE is a serious, life-threatening disorder and the second leading cause of death in hospitalized patients with cancer (Grover et al., 2021). VTE consists of deep vein thrombosis (DVT), which typically involves the deep veins of the legs or pelvis, and its complication, pulmonary embolism (PE).
2. Pathophysiology: Endothelial wall damage is thought to relate to atherosclerotic events such as VTE. This is supported by the fact that VTE occurs with a higher incidence in patients treated with VEGF inhibitors (Wang et al., 2018).
3. Incidence
  - a) The risk of VTE in patients with cancer ranges widely and is based on various factors, such as type of cancer, stage of cancer, medical comorbidities, and type of treatment (Grilz et al., 2018; Horowitz & Brenner, 2020).
  - b) For example, patients with pancreatic cancer can have rates of VTE as high as 20% (Grover et al., 2021).
  - c) The treatment regimen can also play a factor in VTE risk. In patients with multiple myeloma, the incidence of VTE associated with thalidomide alone is relatively low (approximately 3%) (Wang et al., 2018).
  - d) However, the addition of thalidomide to a multiagent chemotherapy regimen, including dexamethasone, can increase that risk to 20%–28% (Grover et al., 2021).

#### 4. Risk factors

- a) A variety of anticancer agents have been shown to increase the risk of thrombotic events in patients with cancer (Canale et al., 2019; Oppelt et al., 2015; Wang et al., 2018).
- b) Treatment with platinum-based agents (e.g., cisplatin, carboplatin, oxaliplatin), immunomodulatory agents (e.g., thalidomide, lenalidomide, pomalidomide), anti-epidermal growth factor receptor antibodies (e.g., cetuximab, panitumumab, necitumumab), VEGF-targeted molecules (e.g., bevacizumab, aflibercept), and TKIs (e.g., sunitinib, sorafenib, axitinib) are associated with a significantly increased risk of VTE (Grover et al., 2021).
- c) Patients with pancreatic, lung, or gastric cancers and those with metastatic cancers have the highest incidence of VTE (Wang et al., 2018). Other risk factors are edema, immobility, dehydration, congestive heart failure, and erythropoiesis-stimulating agents (Grover et al., 2021).

5. Clinical manifestations: Unilateral pain, redness, and swelling of the affected extremity are manifestations of DVT. PE symptoms include shortness of breath, cough, and chest pain.

6. Assessment: Obtain a health history at every clinic or hospital visit. Assess patients for signs and symptoms of VTE, such as pain, redness, and swelling of extremities, especially unilaterally, as well as shortness of breath, cough, and chest pain.

#### 7. Collaborative management

- a) Refer patients for diagnostic testing (e.g., venous Doppler study, computed tomography angiography). Initiate anticoagulant therapy when indicated and monitor therapeutic levels when necessary.
- b) Discontinue medications thought to contribute to VTE.

#### 8. Patient and family education (Wang et al., 2018)

- a) Teach patients the signs and symptoms of vascular complications.
- b) Teach lifestyle changes that may reduce the incidence and severity of vascular complications, such as smoking cessation, low-fat diet, moderate exercise, and stress management.
- c) Advise patients to report symptoms to healthcare providers so that assessment and preventive strategies can be implemented early.

#### E. Coronary artery disease

##### 1. Myocardial ischemia

- a) Several cancer treatments, including cytotoxic drugs, targeted therapies, and radiation therapy, are associated with an increased risk of coronary artery disease with or without acute coronary syndromes.
- b) The most common cancer therapies associated with myocardial infarction and myocardial isch-



emia are angiogenesis inhibitors (e.g., lenalidomide, thalidomide), antimetabolites (e.g., capecitabine; 5-fluorouracil), antimicrotubule agents (e.g., docetaxel, ixabepilone, paclitaxel), monoclonal antibody TKIs (e.g., bevacizumab), proteasome inhibitors (e.g., carfilzomib), and small molecule TKIs (e.g., erlotinib, imatinib, nilotinib, pazopanib, ponatinib, ramucirumab, regorafenib, sorafenib, ziv-aflibercept).

## 2. Pathophysiology

- a) The exact mechanism of cardiotoxicity resulting in myocardial ischemia associated with these agents is not entirely understood. Potential mechanisms include coronary artery thrombosis, coronary arteritis, coronary vasospasm, direct toxic effects, interaction with the coagulation system, autoimmune responses, and apoptosis of the myocardial cells and endothelium, mimicking toxic myocarditis (Caforio et al., 2017).
- b) Myocarditis-induced edema of myocytes creates increased automaticity and impaired perfusion. Increased workload and myocardial stress are thought to be the mechanism for myocardial ischemia and infarction. Thromboses resulting from an increased propensity for clotting may involve coronary arteries (Palaskas et al., 2020).

## 3. Incidence

- a) 5-Fluorouracil: Incidence of myocardial ischemia is 1%–68%.
  - (1) It occurs within two to five days after initiating treatment and presents as angina-like chest pains; however, myocardial infarction, arrhythmias, heart failure, cardiogenic shock, and sudden death have been reported (Chang, Moudgil, et al., 2017; Okwuosa et al., 2017).
  - (2) Cardiac mortality rate with 5-fluorouracil is 2.2%–13%.
- b) Capecitabine: Incidence of cardiotoxicity is 3%–9%. The onset of anginal symptoms ranges from three hours to four days after therapy (Chang, Moudgil, et al., 2017).
- c) Antimicrotubule agents: Incidence of myocardial ischemia is 0.5%–5% with paclitaxel and 1.7% with docetaxel (Chang, Moudgil, et al., 2017).
- d) Monoclonal antibody TKIs (e.g., bevacizumab): Incidence of high-grade ischemia is 0.6%–1.5% (Moslehi & Deininger, 2015).
- e) Small molecule TKIs (e.g., erlotinib, sorafenib): Incidence of myocardial infarction and ischemia is 2.3% when erlotinib is combined with gemcitabine (Mudd et al., 2021). Sorafenib is associated with myocardial infarction in 2.7%–3% of patients (Moslehi & Deininger, 2015).

## 4. Risk factors

- a) Cancer therapies associated with myocardial ischemia, including bevacizumab, bortezomib, capecitabine, docetaxel, doxorubicin, erlotinib, 5-fluorouracil, hydroxyurea, paclitaxel, pazopanib, rituximab, and sorafenib (Okwuosa et al., 2017)
- b) Androgen deprivation (Hu et al., 2020)
- c) Cetuximab used for locally advanced squamous cell head and neck cancer: Similar events were not observed with cetuximab when treating metastatic colorectal cancer (ImClone, 2016).
- d) Interleukin-2 resulting in capillary permeability with myocarditis (Muehlbauer et al., 2018)
- e) Taxane therapy: Few patients suffer coronary artery disease with now-established drug monitoring and dose attenuation plans (Han et al., 2019).
- f) Agents enhancing hypercoagulability: No relationship to any specific chemotherapy or immunotherapy agent has been demonstrated (Grover et al., 2021).
- g) High-dose chemotherapy: Patients may present with rare unexplained chest pain with ischemic ECG changes that spontaneously resolve without medical intervention (Caforio et al., 2017).
- h) Aromatase inhibitors (Okwuosa et al., 2017)
- i) Transarterial chemoembolization with unclear etiology (Wang et al., 2018)

## 5. Clinical manifestations

- a) General signs and symptoms: anxiety, generalized fatigue and weakness, restlessness, agitation
- b) Cardiovascular: retrosternal chest discomfort, tachycardia, new murmur or S<sub>2</sub> or S<sub>3</sub>, congestive heart failure symptoms, hypertension or hypotension
- c) Gastrointestinal: nausea, abdominal pain, indigestion, vomiting
- d) Neurologic: light-headedness, near syncope, syncope
- e) Pulmonary: dyspnea, wheezing, tachypnea, pulmonary rales
- f) Integumentary: diaphoresis; cool, clammy skin; pallor
- g) Elevated cardiac enzymes indicative of myocardial infarction (Caforio et al., 2017)
- h) Ischemic ECG changes in up to 68% of patients (Caforio et al., 2017)

## 6. Assessment

- a) Dysrhythmias are common in patients with cancer; life-threatening ventricular tachycardia or ventricular fibrillation is most common in the first two hours.
- b) Cardiac enzymes (e.g., creatine phosphokinase-MB, troponin I, troponin T) measured in the serum are elevated when a myocardial injury occurs (Han et al., 2019).

- c) Echocardiogram or multigated acquisition scan to assess for left ventricular ejection fraction (LVEF)
  - d) Diagnostic right heart catheterization to measure cardiac output and pulmonary capillary wedge pressure.
7. Collaborative management (Han et al., 2019)
- a) Initiate medical treatment as appropriate (e.g., supplemental oxygen; morphine 2–4 mg IV as needed for analgesia; nitroglycerin sublingually as needed for chest pains).
  - b) Administer oxygen at a rate sufficient to maintain oxygen saturation above 90%, unless otherwise contraindicated.
  - c) Observe for dysrhythmias and ischemic changes, low oxygen saturation, or extremes in blood pressure.
  - d) Obtain an order for aspirin 325 mg to be chewed as soon as a 12-lead ECG is performed and ST changes are present. Administer with caution in patients with low platelet counts and brain metastases.
  - e) Consider patient candidacy for reperfusion strategies, such as cardiac catheterization with angioplasty, stent placement, or intracoronary/IV thrombolysis (Iannaccone et al., 2018).
  - f) Consider ischemia-reducing or myocardial preservation strategies, such as the administration of nitrates, beta-blockers, or statins (Okwuosa et al., 2017; Wang et al., 2017).
  - g) Maintain potassium greater than 4 mEq/L, magnesium greater than 2 mEq/L, and ionized calcium greater than 1 mEq/L (Iannaccone et al., 2018).
  - h) Consider discontinuation of antineoplastic agents thought to cause cardiac ischemia or infarction, such as fluoropyrimidines, oxaliplatin, sorafenib, or tamoxifen.
  - i) Determine the need for follow-up assessment of coronary arteries and myocardial function with exercise stress testing, cardiac catheterization, echocardiogram, or multigated acquisition scan (Han et al., 2019).
  - j) Aggressively manage cardiac risk factors (e.g., hypertension, hyperlipidemia).
  - k) Management of coronary artery disease in patients with cancer needs interprofessional cooperation to formulate a reasonable and individualized plan with special consideration for anticancer therapy (Han et al., 2019).
8. Patient and family education
- a) Explain the disease process, diagnostic tests, and medications to patients and families.
  - b) Provide emotional support to patients and families to lower their level of anxiety, which can reduce heart rate and myocardial oxygen demand.
  - c) Provide instruction regarding risk factor modification (Anderson et al., 2017).
  - d) Educate patients and families regarding reportable symptoms, such as chest discomfort, left arm or neck pain, and dyspnea.
  - e) Educate patients and families regarding managing risks for cardiac ischemia specific to oncology (e.g., anemia, cardiac demands of infection, electrolyte disturbances).
  - f) Include patient teaching on cardiac medications and unique considerations in oncology care (e.g., the risk for low blood pressure increased when febrile; electrolyte disturbances with nausea and vomiting may contribute to cardiac dysrhythmias).
  - g) Provide referrals and education regarding cardiac rehabilitation programs (Anderson et al., 2016).
- F. Left ventricular dysfunction and heart failure
1. Definition
- a) Heart failure is defined as an inadequate contractile force to eject the required amount of blood for perfusion of the body (Hunt et al., 2009; Lindenfeld et al., 2010).
  - b) It is classified as primary or secondary based on the primary etiology and has three types: acute, early-onset progressive, or chronic late progressive (Metra & Teerlink, 2017).
  - c) A consensus definition for cardiotoxicity-induced cardiomyopathy and heart failure is lacking. Multiple definitions include the following:
    - (1) The National Cancer Institute (n.d.) broadly defines cardiotoxicity as “toxicity that affects the heart.”
    - (2) The *Common Terminology Criteria for Adverse Events* defines left ventricular dysfunction and heart failure based on severity (grades 1–5), with a decrease in LVEF of 10% or greater from baseline or LVEF less than 50% (National Cancer Institute Cancer Therapy Evaluation Program, 2017).
      - (a) Grade 1: asymptomatic with laboratory values (e.g., brain natriuretic peptide) or cardiac imaging abnormalities
      - (b) Grade 2: symptoms with moderate activity or exertion
      - (c) Grade 3: symptoms at rest or with minimal activity or exertion
      - (d) Grade 4: life-threatening consequences, urgent intervention indicated
      - (e) Grade 5: death

- (3) The Cardiac Review and Evaluation Committee supervising trastuzumab clinical trials defined drug-related cardiotoxicity as one or more of the following (Bloom et al., 2016):

- (a) Cardiomyopathy characterized by a decrease in LVEF, either global or more severe in the septum
- (b) Symptoms associated with congestive heart failure
- (c) Signs associated with congestive heart failure (e.g., S<sub>3</sub> gallop, tachycardia, both)
- (d) Reduction in LVEF from baseline of at least 5% to less than 55%, with accompanying signs or symptoms of congestive heart failure, or a reduction in LVEF of at least 10% to less than 55% without accompanying signs or symptoms

- (4) The U.S. Food and Drug Administration defined anthracycline-induced cardiotoxicity as a greater than 20% decrease in LVEF when the baseline is normal or a greater than 10% decrease when the baseline is not normal (Bloom et al., 2016).

- (5) The American Society of Echocardiography and European Association of Cardiovascular Imaging defined cancer therapeutics-related cardiac dysfunction as a decrease in LVEF of more than 10% to a value less than 53% confirmed by repeat imaging (Bloom et al., 2016; Plana et al., 2014).

## 2. Pathophysiology

### a) Anthracycline-induced cardiotoxicity

- (1) The exact mechanism is not fully understood, although multiple pathways have been implicated (McGowan et al., 2017).
- (2) The most commonly accepted pathophysiologic mechanism is the oxidative stress hypothesis, which suggests that the generation of reactive oxygen species and lipid peroxidation of the cell membrane damage cardiomyocytes.
- (3) Other proposed mechanisms include intercalation into nuclear DNA to impair protein synthesis and inhibition of topoisomerase II to inhibit DNA repair (Franco & Lipshultz, 2015; Sawicki et al., 2021).
- (4) Several agents have been identified as potentially effective prophylaxis for anthracycline-induced cardiotoxicity, including beta-blockers, statins, angioten-

sin antagonists, and dexrazoxane (Sawicki et al., 2021).

- (a) Dexrazoxane is a topoisomerase II beta inhibitor that converts an active ion-binding form to prevent toxic radical injury. The recommended dosing ratio of dexrazoxane to doxorubicin is 10:1 (Wolters Kluwer Health, 2021).

- (b) Dexrazoxane is reconstituted with sterile water and may be further diluted with lactated Ringer's solution for rapid IV infusion; it should not be administered via IV push (Wolters Kluwer Health, 2021).

### b) Targeted therapy-associated toxicity

- (1) The mechanisms of action proposed for targeted therapy-associated toxicity (e.g., trastuzumab) are typically related to either on- or off-target adverse reactions, such as left ventricular dysfunction or heart failure.

- (2) On-target toxicity occurs when the specific kinase targeted by the therapy provides an important physiologic function in addition to the target tumor tissue (Chaar et al., 2018). An example of on-target toxicity is cardiotoxicity that may occur with trastuzumab. It is believed that trastuzumab interferes with HER2 functioning in cardiac tissue, which manifests as left ventricular systolic dysfunction (Herrmann, 2020).

- (3) Off-target toxicity is observed when a nonselective TKI modulates the function of a kinase involved in normal vascular physiology and is not the target in cancer cells (Herrmann, 2020). A typical example is the unintended inhibition of the AMP-activated protein kinase (known as AMPK) by sunitinib, a mechanism that may be partially responsible for cardiomyopathy.

3. Incidence (Cardinale et al., 2020; McGowan et al., 2017; Zamorano et al., 2016)

- a) Cardiotoxicities resulting in left ventricular dysfunction or cardiomyopathy and heart failure are relatively common and serious side effects of cancer treatment. Heart failure due to cancer therapy has been linked to a 3.5-fold increased mortality risk compared with idiopathic cardiomyopathy (Bloom et al., 2016).

- b) Anthracyclines produce some degree of cardiac dysfunction in 50% of patients over a 10–20-year period after exposure. Approximately 3%–5%

develop overt heart failure (McGowan et al., 2017). Anthracycline-induced left ventricular dysfunction or heart failure may be classified as the following:

- (1) Acute-onset anthracycline-induced toxicity, which develops in 1% of patients, presents immediately after infusion and manifests as supraventricular arrhythmia, ECG changes, and transient decline in myocardial contractility, which is usually present and reversible.
  - (2) Early-onset, chronic progressive, anthracycline-induced cardiotoxicity occurs during therapy or within the first year after treatment in 1.6%–2.1% of patients (Cardinale et al., 2020).
  - (3) Late-onset, chronic progressive, anthracycline-induced cardiotoxicity occurs one year or later after completion of therapy in 1.6%–5% of patients. Late-occurring cardiotoxicity may not be clinically evident until 10–20 years after the first dose of treatment (Bloom et al., 2016; Cardinale et al., 2020), with a median of 7 years after treatment (Zamorano et al., 2016).
- c) Trastuzumab-induced cardiotoxicity does not appear to be cumulative dose dependent and is associated with reversible cardiomyocyte dysfunction, which typically recovers after treatment discontinuation of the targeted agent and initiation of heart failure therapy (Nemeth et al., 2017).
- (1) Patients who received the combination therapy of trastuzumab with anthracyclines have a higher chance of developing left ventricular dysfunction or heart failure (Nemeth et al., 2017).
  - (2) Adjuvant trastuzumab after anthracyclines and paclitaxel is associated with a 4%–18.6% incidence of left ventricular dysfunction and 1.6%–3.3% incidence of heart failure (Nemeth et al., 2017).
- d) Bevacizumab, a humanized monoclonal antibody against VEGF, has an adverse complication of heart failure (14% incidence) (Wolters Kluwer Health, 2021).
4. Risk factors
- a) Anthracycline-induced cardiotoxicity (Cardinale et al., 2020)
    - (1) Lifetime cumulative dose (Camp-Sorrell, 2018)
    - (2) Infusion regimen
    - (3) Preexisting cardiac disease
    - (4) Preexisting hypertension
    - (5) Concomitant use of other chemotherapy agents known to cause cardiotoxicity (e.g., cyclophosphamide, trastuzumab, paclitaxel)
    - (6) History of prior mediastinal radiation therapy
    - (7) Female sex
    - (8) Age younger than 5 years or older than 65 years
    - (9) Increased length of time since completion of chemotherapy
    - (10) Increase in biomarkers (e.g., troponins, natriuretic peptides) during and after administration (Zamorano et al., 2016)
  - b) Trastuzumab-induced cardiotoxicity (Dempsey et al., 2021)
    - (1) Age older than 50 years
    - (2) Borderline LVEF before treatment
    - (3) History of cardiovascular disease
    - (4) Presence of cardiovascular risk factors (e.g., diabetes, dyslipidemia, elevated body mass index greater than 30 kg/m<sup>2</sup>)
    - (5) Prior treatment with anthracyclines
    - (6) Genetic predisposition and immune status
5. Clinical manifestation (Metra & Teerlink, 2017)
- a) Signs
    - (1) Edema: lower-extremity swelling, abdominal ascites
    - (2) Jugular venous distension
    - (3) Hepatomegaly: enlarged liver
    - (4) Abnormal heart sounds: S<sub>3</sub> gallop, murmurs
    - (5) Tachycardia
    - (6) Hypotension
    - (7) Tachypnea
    - (8) Abnormal lung sounds: crackles
  - b) Symptoms
    - (1) Fatigue, weakness, exercise intolerance
    - (2) Dyspnea
    - (3) Orthopnea
    - (4) Paroxysmal nocturnal dyspnea
    - (5) Increased abdominal girth
    - (6) Frequent coughing, especially at night when lying flat
    - (7) Sudden weight gain
6. Assessment
- a) Perform a comprehensive history and physical assessment.
  - b) Obtain a history of treatments received for cancer therapy.
  - c) Determine the etiology of heart failure (e.g., ischemic vs. nonischemic).
  - d) Classify the presenting syndrome (e.g., acute vs. chronic; systolic vs. diastolic).
  - e) Identify concomitant disease relevant to heart failure (e.g., amyloidosis, hemochromatosis).

- f) Evaluate for the presence of coronary artery disease and valvular problems.
  - g) Assess the severity of symptoms.
  - h) Perform diagnostic and interventional procedures as needed (e.g., cardiac catheterization).
7. Collaborative management and prevention (Metra & Teerlink, 2017)
- a) Identify precipitating factors for acute decompensated heart failure.
    - (1) Patient-related factors
      - (a) Nonadherence to medications
      - (b) Excessive salt intake
      - (c) Physical and environmental stressors
    - (2) Cardiac-related factors
      - (a) Cardiac arrhythmias (e.g., atrial fibrillation, ventricular fibrillation, bradyarrhythmias)
      - (b) Uncontrolled hypertension
      - (c) Acute myocardial infarction
      - (d) Valvular disease, worsening mitral regurgitation
    - (3) Caution with concomitant medications
      - (a) Steroids
      - (b) Chemotherapy (e.g., doxorubicin, cyclophosphamide)
      - (c) Nonsteroidal anti-inflammatory drugs
      - (d) Thiazolidinediones
  - b) Establish the diagnosis of left ventricular dysfunction or heart failure.
    - (1) Echocardiography to assess left ventricular function
    - (2) Chest x-ray to evaluate for pulmonary edema, pleural effusion, and cardiomegaly
    - (3) Nuclear imaging to detect the location and severity of coronary artery disease
    - (4) Coronary angiography to evaluate coronary artery disease
    - (5) Endomyocardial biopsy to diagnose anthracycline-induced cardiomyopathy
    - (6) Thyroid profile to evaluate for hypothyroidism or hyperthyroidism as heart failure etiology
    - (7) Viral titers to evaluate causes of myocarditis, endocarditis, and pericarditis
    - (8) Iron studies to evaluate for hemochromatosis resulting in heart failure
  - c) Commonly recommended pharmacologic therapies for heart failure include the following:
    - (1) Angiotensin-converting enzyme inhibitors
    - (2) Angiotensin receptor blocker
    - (3) Aldosterone antagonists
    - (4) Cardiac glycosides
    - (5) Direct-acting vasodilator
8. Patient and family education
- a) Dietary modifications: Instruct patients on sodium restriction to 2,000 mg daily to prevent volume overload.
  - b) Physical activity: Encourage physical activity, except during periods of acute exacerbation when physical rest is recommended.
  - c) Weight monitoring: Patients should be advised to perform daily weight monitoring and notify their healthcare provider in case of sudden and unexpected weight gain (more than 2 pounds per day for two consecutive days or more than 5 pounds per week) for possible adjustment of diuretic dose.
  - d) Alcohol intake: Moderate intake (one drink per day for women and two drinks per day for men) is permitted except in cases of alcoholic cardiomyopathy.
  - e) Encourage smoking cessation.
- G. Myocarditis
1. Definition: Myocarditis is an infrequent but often lethal cardiac complication characterized by inflammation of the myocardium, resulting from anticancer therapeutics commonly referred to as immune checkpoint inhibitors or blockers (Ribas & Wolchok, 2018).
  2. Pathophysiology
    - a) The precise mechanisms by which immune checkpoint inhibitors cause cardiotoxicity remain undefined (Moslehi et al., 2021).
    - b) Suggested mechanisms include a shared antigen between the tumor and myocardium, T-cell receptor targeting a different but homologous muscle antigen as the tumor antigen, or certain T-cell receptors targeting dissimilar antigens (Johnson et al., 2016).
  3. Incidence
    - a) The true incidence of myocarditis associated with immune checkpoint inhibitors is likely underestimated due to a combination of factors, including the lack of specificity in the clinical presentation, the potential of overlap with other cardiovascular and general medical illnesses, the challenges in the diagnosis, and a general lack of awareness of this condition (Ganatra & Neilan, 2018; Moslehi et al., 2021).
    - b) Reports suggest that the incidence of immune checkpoint inhibitor-associated myocarditis is 0.27%–1.14% (Johnson et al., 2016; Mahmood et al., 2018). However, the true incidence may be higher, as initial reports identified only severe cases (Norwood et al., 2017).
    - c) The prevalence of immune checkpoint inhibitor-associated myocarditis is higher with



combination immunotherapies. Pharmacovigilance data suggest that a combination of ipilimumab and nivolumab is accompanied by a 4.74-fold risk of myocarditis compared with nivolumab alone (Johnson et al., 2016).

#### 4. Risk factors

- a) Combination therapy of anti-cytotoxic T-lymphocyte antigen 4 and anti-programmed cell death protein 1 agents appears to be the strongest risk factor.
- b) Cardiac-related, immune-related, and cancer-related risk factors impact the risk for immune checkpoint inhibitor-associated myocarditis (Wang et al., 2017).
- c) Genetic variation, including germline or somatic (i.e., in the tumor), may contribute to the development of immune checkpoint inhibitor-associated myocarditis (Moslehi et al., 2021).

#### 5. Clinical manifestations

- a) The clinical presentation of immune checkpoint inhibitor-associated myocarditis is variable. Myocarditis typically occurs early, with elevated troponin, may present with a normal LVEF, and may have a fulminant course.
- b) Fulminant cases are characterized by early onset following treatment, arrhythmias and conduction disturbances, concomitant skeletal myositis and myasthenia gravis, and sudden death (Escudier et al., 2017; Mahmood et al., 2018; Moslehi et al., 2018; Salem et al., 2018).
- c) Diagnosing myocarditis in patients treated with immune checkpoint inhibitors can be challenging. A multipronged approach has been proposed to rule out other causes for symptomatology, such as acute coronary syndromes.
- d) Diagnostic tests can include a combination of cardiac biomarkers, cardiac imaging, and endomyocardial biopsy (Bonaca et al., 2019).
- e) Endomyocardial biopsy is considered the gold standard for diagnosing myocarditis (Caforio et al., 2017; Moslehi et al., 2019). The histopathologic features of immune checkpoint inhibitor-associated myocarditis involve myocardial infiltration of T lymphocytes (cluster of differentiation [CD]4+ and CD8+) and macrophages, and myocyte death (Johnson et al., 2016).

#### 6. Assessment

- a) Assess for symptoms of myocarditis, which include chest pain, fatigue, fast or abnormal heartbeat, shortness of breath, and lower extremity edema.
- b) Currently, no consensus exists regarding screening, surveillance, prevention, or treatment strate-

gies for immune checkpoint inhibitor-associated myocarditis (Moslehi et al., 2021).

- c) Baseline ECG and troponin levels are recommended in all patients (Ganatra & Neilan, 2018; Hu et al., 2019; Neilan et al., 2018; Wang et al., 2017).
- d) High-risk patients should undergo surveillance with serum troponin measurements after the initiation of treatment (Shafi et al., 2017).

#### 7. Collaborative management and prevention

- a) Treatments for myocarditis have been largely extrapolated from therapies for noncardiac immune checkpoint inhibitor-associated toxicities, including cessation of immune checkpoint inhibitors, supportive management, and glucocorticoids (Brahmer et al., 2018).
- b) Administer high steroid doses (e.g., methylprednisolone 1 g/kg), followed by a four- to six-week taper upon symptom improvement (Zhang et al., 2020).
- c) Consider initiating other immune modulators if patients are not responding clinically to steroids (Arangalage et al., 2017; Esfahani et al., 2019; Mahmood et al., 2018; Palaskas et al., 2020; Salem et al., 2018; Tay et al., 2017).
  - (1) Infliximab
  - (2) IV immunoglobulin
  - (3) Plasmapheresis
  - (4) Abatacept
  - (5) Alemtuzumab
  - (6) Antithymocyte globulin
  - (7) Mycophenolate

#### 8. Patient and family education

- a) Instruct patients that it is important to stay in close contact with their treatment center during immune checkpoint inhibitor therapy.
- b) Instruct patients that they will be monitored closely to detect potential immune-related adverse effects and to see how well immunotherapy is working against their cancer.
- c) Instruct patients that immune-related adverse events can range from mild to life threatening, can occur during or after treatment, and may affect one or more organ systems.
- d) Instruct patients regarding the side effects of steroid therapy, which include increased appetite, weight gain, mood changes, water retention, and high blood pressure.
- e) Corticosteroid therapy should not be discontinued suddenly. The healthcare team will instruct patients on lowering the dose slowly over several weeks.
- f) Oral corticosteroids can weaken the immune system's ability to fight fungal and *Pneumocystis jirovecii* pneumonia infections. The provider may prescribe an antifungal medica-

tion, such as fluconazole, and prophylaxis with trimethoprim-sulfamethoxazole.

- g) Patients treated with immune checkpoint inhibitors may be provided a wallet card that states the type of immunotherapy received, potential side effects, and contact numbers for the cancer care team.
- h) Instruct patients to notify all healthcare providers involved in their care that they are receiving or have received immunotherapy.

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## CHAPTER 17

# Pulmonary Toxicities

### A. Overview

1. Pulmonary toxicity ranges from reversible short-term reactive airway disease to diffuse permanent fibrosis and structural destruction.
  - a) Cytotoxic drugs are a leading cause of pulmonary toxicity and account for 23%–51% of cases of drug-induced interstitial lung disease (ILD) (Conte et al., 2022; Skeoch et al., 2018). On rare occasions, these toxicities are fatal (Abdel-Rahman & Elhalawani, 2015; Kaku et al., 2022; Osawa et al., 2015).
  - b) The onset of pulmonary toxicities is variable and may occur acutely, within hours to days, or may be more long term, after many months to years (Skeoch et al., 2018; Thalambedu & El-Habr, 2020).
  - c) Pulmonary toxicities can occur as a consequence of chemotherapy, targeted therapy, or immunotherapy, with increasing risk and severity with combination therapies (Iwashita et al., 2021; National Comprehensive Cancer Network [NCCN], 2022a).
  - d) Drug-induced ILD is the most prevalent of the drug-induced pulmonary toxicities.
  - e) Additional pulmonary toxicities are emerging as multitargeted therapies become more common.
2. Determining the etiology of pulmonary signs and symptoms in patients with cancer can be challenging because drug-induced toxicity can mimic a broad spectrum of pathogenic causes, including infection and neoplasm (Leger et al., 2017). Consequently, it is imperative to understand the potential for toxicity and to detect pulmonary toxicity as early as possible.
  - a) Common symptoms of pulmonary toxicities are dyspnea, cough, chest pain, low-grade fever, and fatigue (Conte et al., 2022; Johkoh et al., 2021; NCCN, 2022a; Rapoport et al., 2021).
  - b) A computed tomography (CT) scan is the primary diagnostic test used to differentiate specific pulmonary conditions. However, histologic sampling may be necessary to determine the precise

pathology (Conte et al., 2022; Johkoh et al., 2021; Rapoport et al., 2021).

### B. ILD

1. ILD is a heterogeneous group of lung disorders involving damage to the alveoli and surrounding interstitium that culminates in inflammation and fibrosis. ILD includes acute chemotherapy-induced pneumonitis, pulmonary capillary permeability syndrome, chemotherapy-related acute respiratory distress syndrome, hypersensitivity/eosinophilic pneumonitis, cryptogenic (of unknown cause) organizing pneumonia, pulmonary fibrosis, and pulmonary alveolar proteinosis (Jouneau et al., 2020; Samarelli et al., 2021).
2. Pathophysiology
  - a) Postulated pathologic changes (Cottin, 2016; Jouneau et al., 2020; Podolanczuk et al., 2021; Samarelli et al., 2021)
    - (1) Injury to the lung parenchyma
    - (2) Inflammation of alveoli, alveolar cell walls, interstitial spaces, and terminal bronchioles
    - (3) Release of interleukins and transforming growth factors
    - (4) Destruction of the alveolar-capillary endothelium, leading to changes in interstitial fibroblasts
    - (5) Activation of fibroblasts and myofibroblasts, causing collagen deposition in the alveolar interstitium
    - (6) Pulmonary alveolar proteinosis–like changes, which may occur with long-term interstitial pneumonitis and may be linked to the severity of the disease
  - b) The disease results predominantly from inflammatory features (Samarelli et al., 2021).
    - (1) Fluid or bloody exudates in alveoli
    - (2) Fluid between alveoli (interstitial spaces) from the degradation of the alveolar wall
    - (3) Fibrosis and stiffening of vascular, airway, and alveolar walls

- c) Immune checkpoint inhibitors create a T-cell hyperexpansion with immune hyperactivity (Possick, 2017; Rapoport et al., 2021; Shannon et al., 2020).
    - (1) Direct interaction of T cells with healthy tissues
    - (2) High levels of cluster of differentiation (CD) 4 helper T cytokines and increased migration of cytolytic CD8 T cells and organ damage
    - (3) Programmed cell death-ligand 2 localized to antigen-presenting cells (e.g., macrophages) with toxic lung effects
    - (4) Direct lung injury caused by cytokines
  - d) Resolution results in scarring and fibrosis of tissue, beginning in the interstitium and later involving the alveolar sacs. Pulmonary fibrosis is the chronic continuation of some acute pneumonitis syndromes.
  - e) Stiff, noncompliant lungs have poor elasticity, which increases the work of breathing.
  - f) Chronic exposure to chemotherapy agents may result in changes in lung connective tissue, obliteration of alveoli, and dilation of air spaces, leading to a honeycomb appearance on x-rays and scans (Diederich, 2016).
  - g) Increased pulmonary pressure from connective tissue and fibrotic banding leads to pulmonary hypertension, cor pulmonale, and heart failure (Mathai & Danoff, 2016).
  - h) Cellular mechanisms of injury
    - (1) Direct damage: Some chemotherapy agents (e.g., high-dose cytarabine, bleomycin, mitomycin C) cause direct damage to the alveoli and capillary endothelium (Madabhavi et al., 2017; Saijo, 2018).
    - (2) Metabolic damage: Cyclophosphamide metabolism in the lung leads to the formation of alkylating metabolites and acrolein, which may cause toxicity (Patel, 1990).
    - (3) Multikinase inhibitors (e.g., sorafenib), including tyrosine kinase inhibitors (e.g., imatinib, dasatinib), and epidermal growth factor receptor inhibitors (e.g., cetuximab, panitumumab) impede alveolar repair mechanisms that can enhance the effect of previous lung injury (Vahid & Marik, 2008).
    - (4) Immune checkpoint inhibitors may produce a unique physiologic autoimmune response that results in interstitial pneumonitis, but exact mechanisms of pathology remain unclear. Incidence may increase when immune checkpoint inhibitors are given in combination with chemotherapy agents (Possick, 2017; Shannon et al., 2020; Teuwen et al., 2015).
  - (5) Acute onset of pulmonary edema (noncardiogenic) is related to cytokine-induced capillary leak syndrome (Siddall et al., 2017).
  - (6) Hemorrhagic pneumonitis is a parenchymal injury with microvascular bleeding similar to alveolar hemorrhage that occurs in alveolar and interstitial spaces (J.A. Park, 2021).
  - (7) Hypersensitivity pneumonitis is characterized by an acute, rapid-onset immunologic alveolar reaction that leads to capillary permeability, fluid extravasation, and lymphocytic or eosinophilic infiltration of the alveoli and interstitium, impeding gas exchange (Raghu et al., 2020).
  - (8) Cryptogenic organizing pneumonia, previously called bronchiolitis obliterans organizing pneumonia, is characterized by the development of fibrous connective tissue between and involving alveolar and bronchiolar spaces, inflammatory activation of autoimmune collagen deposition, and obstruction of the ventilating airways (Bellanger et al., 2015). It has been reported in patients with breast and lung cancer receiving chemoradiation (Epler & Kelly, 2020; Falcinelli et al., 2015).
  - (9) Pulmonary alveolar proteinosis (PAP) is a syndrome in which alveolar macrophages are dysfunctional, causing surfactant proteins and lipids to accumulate in the pulmonary alveoli and impeding gas exchange. Although the triggering mechanisms are not well understood, autoimmune activation is suspected. It is characterized by granulocyte macrophage-colony-stimulating factor deficiency. In hematologic malignancies, it is classified as secondary PAP, particularly myelodysplastic syndromes. It is unclear if it is triggered by medication exposure or immune deficits (Jouneau et al., 2020).
3. Incidence: ILD incidence varies based on the individual patient and medication-related factors. Pneumonitis syndromes are infrequent.
    - a) Incidence increases when pulmonary-toxic agents are administered concomitantly with thoracic irradiation (Arroyo-Hernández et al., 2021).
    - b) Incidence is influenced by cumulative dose with some agents (Leger et al., 2017).



- c) Combining agents with similar pulmonary toxicities may enhance the risk for adverse effects (Leger et al., 2017; Teuwen et al., 2015).
  - d) The incidence of pneumonitis is higher in specific populations, even when equivalent drug exposure has been experienced. Immune checkpoint inhibitor-induced pneumonitis is more common among patients with lung cancer and renal cell cancer than those with melanoma (Possick, 2017; Shannon et al., 2020) and when combination immune checkpoint inhibitor therapy is administered (Gutierrez et al., 2020).
4. Risk factors
- a) General patient-specific risk factors (Ariad Pharmaceuticals, 2022; Handa et al., 2018; Podolanczuk & Putman, 2021)
    - (1) Advancing age causes an imbalance of cell types that can cause architectural distortion and the inability to cope with cumulative environmental insults (Schneider et al., 2021). This can lead to a susceptibility to pulmonary toxicity from certain cytotoxic drugs (Handa et al., 2018; Koshikawa et al., 2020).
    - (2) Tobacco smoking is associated with inflammation in the lung parenchyma (Dawod et al., 2020; Handa et al., 2018; Podolanczuk & Putman, 2021).
    - (3) Deteriorating creatinine clearance that affects drug clearance can increase the risk of developing ILD (Handa et al., 2018; Koshikawa et al., 2020).
    - (4) Previous treatment with bleomycin had been known to increase the risk of pulmonary complications in the postoperative setting. It is generally accepted that oxygen administration can increase the risk of bleomycin toxicity, and the standard practice is to limit oxygen administration. However, it remains unclear whether the threshold and duration of oxygen therapy can increase toxicity in patients treated with bleomycin (Aakre et al., 2014).
    - (5) Prior lung disease (e.g., chronic obstructive pulmonary disease) or reduced lung reserve can increase the risk of ILD development (Handa et al., 2018; Willemsen et al., 2016).
    - (6) Autoimmune disease enhances the release of inflammatory mediators that increase drug-related pulmonary toxicity (Tewwen et al., 2015).
    - (7) Graft-versus-host disease is a risk factor due to acute and subacute patterns of lung injury (Abugideiri et al., 2016).
  - b) Treatment-related factors (see Table 17-1)
    - (1) The physiologic effects of specific antineoplastic agents on tissues, metabolism, immune activity, and epithelial and endothelial cells can cause the following (Conte et al., 2022; Iwashita et al., 2021; Long & Suresh, 2020).
      - (a) Bronchospasm
      - (b) Noncardiogenic pulmonary edema
      - (c) Hypersensitivity pneumonitis
      - (d) Cryptogenic organizing pneumonia
      - (e) Nonspecific cough and dyspnea
    - (2) It has not been determined whether any single drug is the causative agent or if the interaction of multiple antineoplastic agents results in enhanced toxicity (Desai et al., 2016; Leger et al., 2017).
    - (3) Concurrent chemotherapy and radiation therapy, especially with transplant therapies, has been associated with pneumonitis (Desai et al., 2016; Hanania et al., 2019).
    - (4) Increased toxicity with an increased dose results from drug accumulation in the lung. Two patterns of dose-related pulmonary toxicity are clinically observed (Leger et al., 2017).
      - (a) The threshold effect is the definitive increase in risk for pulmonary toxicity when a cumulative dose is reached.
        - i. Bleomycin: total lifetime dose exceeding 400 units (Hospira, 2021a)
        - ii. Busulfan: in the absence of other predisposing factors, a cumulative dose greater than 500 mg (Matijasic et al., 2019; Otsuka Pharmaceuticals, 2017)
        - iii. Mitomycin C: maximum dose of 30 mg/m<sup>2</sup> (Accord Healthcare, 2018)
        - iv. Lomustine: dose greater than 1,100 mg/m<sup>2</sup> (NextSource Biotechnology, 2018)
      - (b) The linear effect is the risk of increased pulmonary toxicity as more of the drug per dose is administered (e.g., carmustine at a cumulative dose greater than 1,400 mg/m<sup>2</sup>) (Amneal Pharmaceuticals, 2018).
    - (5) Risk with thoracic radiation therapy is related to exposure to ionizing radiation dose and fractionation (Arroyo-Hernández et al., 2021; Bledsoe et al., 2017).

**TABLE 17-1.** Pulmonary Toxicities of Antineoplastic Agents

| Classification             | Drug                                                               | Adverse Effects, Signs, and Symptoms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                             |
|----------------------------|--------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Chemotherapy Agents</b> |                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Alkylating agents          | Busulfan (IV: Busulfex <sup>®</sup> ; oral: Myleran <sup>®</sup> ) | <p>Interstitial pneumonitis, pulmonary fibrosis, organizing pneumonia, pulmonary VOD, insidious onset cough, dyspnea, low-grade fever, bronchopulmonary dysplasia progressing to interstitial pulmonary fibrosis (busulfan lung)</p> <p>Rare incidence of alveolar hemorrhage</p> <p>Bronchopulmonary dysplasia with pulmonary fibrosis is a rare but serious complication following chronic busulfan therapy. The average time to symptom onset is 4 years after therapy.</p> <p>Chest x-rays show diffuse linear densities, sometimes with reticular nodular or nodular infiltrates or consolidation. Pleural effusions have occurred.</p> | <p>Establish baseline pulmonary function. Assess x-rays, PFTs, and computed tomography scans as indicated.</p> <p>Advise patients to report cough or shortness of breath to the healthcare team.</p> <p>(Accord Healthcare, 2021; Hospira, 2021a; Maldonado et al., 2022a; Russi &amp; Negrin, 2022)</p>                                                                                                           |
|                            | Chlorambucil (Leukeran <sup>®</sup> )                              | <p>Interstitial pneumonia, organizing pneumonia, pulmonary fibrosis</p> <p>Pulmonary fibrosis and bronchopulmonary dysplasia in patients receiving long-term therapy</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | <p>Establish baseline pulmonary function.</p> <p>(Aspen Global, 2016)</p>                                                                                                                                                                                                                                                                                                                                          |
|                            | Cyclophosphamide (Cytoxan <sup>®</sup> )                           | <p>Interstitial pneumonitis, pulmonary fibrosis, alveolar hemorrhage</p> <p>Edema, fibrosis, alveolar hemorrhage, and fibrin deposition due to the accumulation of the alkylating agent metabolite acrolein</p> <p>Interstitial pulmonary fibrosis in patients receiving high doses of cyclophosphamide over a prolonged period</p>                                                                                                                                                                                                                                                                                                          | <p>Concomitant oxygen delivery &gt; 60% fraction of inspired oxygen may exacerbate incidence and severity.</p> <p>Treatment involves discontinuing the agent and administering steroids, which have good to variable response in early-onset toxicity. Delayed-onset interstitial fibrosis with pleural thickening is less responsive to corticosteroids.</p> <p>(Ingenus Pharmaceuticals, 2021; Specks, 2022)</p> |
|                            | Ifosfamide (Ifex <sup>®</sup> )                                    | Interstitial pneumonitis, pulmonary fibrosis                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | <p>Methemoglobinemia occurs because of reactions between 4-thioifosfamide and glutathione to deplete antioxidant reserves.</p> <p>Dyspnea, tachypnea, and cough warrant investigation for possible pulmonary toxicity. Advise patients to report symptoms of pulmonary toxicity.</p> <p>(Fresenius Kabi, 2016; Hadjiladis &amp; Govert, 2000; Maldonado et al., 2022a)</p>                                         |
|                            | Melphalan (Alkeran <sup>®</sup> , Evomela <sup>®</sup> )           | <p>Bronchospasm, interstitial pneumonitis</p> <p>Pulmonary fibrosis, interstitial pneumonia, bronchospasm, and dyspnea signal rare hypersensitivity reaction and not pulmonary toxicity.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                 | <p>Advise patients to report symptoms of pulmonary toxicity.</p> <p>Patients respond to antihistamine and corticosteroid therapy.</p> <p>(GlaxoSmithKline, 2012; Maldonado et al., 2022a)</p>                                                                                                                                                                                                                      |
|                            | Oxaliplatin (Eloxatin <sup>®</sup> )                               | <p>Dyspnea of uncertain significance, bronchospasm, hypersensitivity pneumonitis, interstitial pneumonitis, pulmonary fibrosis, diffuse alveolar hemorrhage, organizing pneumonia</p> <p>Rare cases of diffuse alveolar hemorrhage have been fatal.</p> <p>Previously treated patients have experienced subjective sensations of dysphagia or dyspnea without laryngospasm or bronchospasm (no stridor or wheezing).</p>                                                                                                                                                                                                                     | <p>With unexplained respiratory symptoms, such as nonproductive cough, dyspnea, crackles, or radiologic pulmonary infiltrates, oxaliplatin should be discontinued until further investigation excludes ILD or pulmonary fibrosis.</p> <p>(Bellanger et al., 2015; Falcinelli et al., 2015; Sanofi-Aventis U.S., 2020)</p>                                                                                          |

(Continued on next page)



**TABLE 17-1.** Pulmonary Toxicities of Antineoplastic Agents (*Continued*)

| Classification                        | Drug                       | Adverse Effects, Signs, and Symptoms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|---------------------------------------|----------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Chemotherapy Agents (Cont.)</b>    |                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Alkylating agents<br>( <i>Cont.</i> ) | Temozolomide<br>(Temodar®) | Interstitial pneumonitis, alveolitis, pulmonary fibrosis, <i>Pneumocystis</i> pneumonia                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Establish baseline pulmonary function and reassess when any respiratory symptoms occur.<br>Advise patients of the increased risk of <i>Pneumocystis jirovecii</i> pneumonia and to contact their healthcare provider immediately for new or worsening pulmonary symptoms. (Merck, 2022c)                                                                                                                                                                                                                                                                                        |
| Antimetabolites                       | Capecitabine<br>(Xeloda®)  | Interstitial pneumonitis, dyspnea, cough, respiratory distress                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Advise patients to report symptoms of pulmonary toxicity. (Genentech, 2021e)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|                                       | Cytarabine<br>(Cytosar®)   | Noncardiogenic pulmonary edema (previously known as cytarabine syndrome), a syndrome of sudden respiratory distress, rapidly progressing to pulmonary edema, capillary leak syndrome, respiratory failure, and ARDS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Continuous infusion cytarabine is associated with pulmonary toxicity (fluid overload). (Hospira, 2020; Nucci et al., 2015; Sanz & Montesinos, 2014)                                                                                                                                                                                                                                                                                                                                                                                                                             |
|                                       | Fludarabine                | Severe pulmonary toxicity resulting in ARDS, respiratory distress, pulmonary hemorrhage, respiratory failure, pneumonitis, and pulmonary fibrosis<br>Pulmonary hypersensitivity reactions, such as dyspnea, cough, and interstitial pulmonary infiltrate                                                                                                                                                                                                                                                                                                                                                                                                                                             | Avoid concurrent use with pentostatin due to the risk of fatal pulmonary toxicity. (Hospira, 2018a)                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|                                       | Gemcitabine<br>(Gemzar®)   | Pulmonary edema, ILD, pulmonary fibrosis, ARDS<br>The onset of pulmonary symptoms may occur up to 2 weeks after the final dose.<br>Severe pulmonary toxicities (including death) are likely related to bronchospastic events, capillary permeability-induced pulmonary edema, or diffuse alveolar hemorrhage.                                                                                                                                                                                                                                                                                                                                                                                        | Increased toxicity occurs with multiple weekly doses and prolonged infusion time beyond 60 minutes.<br>The drug should be discontinued for unexplained dyspnea or other evidence of severe pulmonary toxicity.<br>Advise patients of the risks of pulmonary toxicity, including respiratory failure and death. Instruct patients to immediately contact their healthcare provider with the development of shortness of breath, wheezing, or cough. (Eli Lilly and Company, 2019b)                                                                                               |
|                                       | Methotrexate               | Hypersensitivity pneumonitis, pulmonary fibrosis, organizing pneumonia; fever, dyspnea, cough (especially dry, nonproductive), nonspecific pneumonitis, or chronic interstitial obstructive pulmonary disease (deaths have been reported); pulmonary infiltrates<br>Acute or chronic interstitial pneumonitis and <i>Pneumocystis jirovecii</i> pneumonia may occur with methotrexate therapy.<br>A higher risk for complications is associated with older age, previous use of disease-modifying immunosuppressive drugs, pre-existing lung disease, abnormal baseline PFTs, daily dosing rather than weekly administration, and decreased elimination of methotrexate (e.g., renal insufficiency). | Methotrexate-induced lung disease, including acute or chronic interstitial pneumonitis, is a potentially dangerous condition that may occur acutely at any time during therapy and has been reported at low doses. It is not always fully reversible, and fatalities have been reported. Pulmonary symptoms (especially a dry, nonproductive cough) may require treatment interruption and careful investigation.<br>PFTs may be useful with suspected methotrexate-induced lung disease, especially if baseline measurements are available. (Balk, 2022; Fresenius Kabi, 2020) |

(Continued on next page)

**TABLE 17-1.** Pulmonary Toxicities of Antineoplastic Agents (*Continued*)

| Classification                     | Drug                                  | Adverse Effects, Signs, and Symptoms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|------------------------------------|---------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Chemotherapy Agents (Cont.)</b> |                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Antimetabolites<br>(Cont.)         | Pemetrexed<br>(Alimta®)               | Interstitial pneumonitis, including fatal cases<br>Alveolar hemorrhage (rare), ILD, and pleural effusions have been reported. Dyspnea, cough, and fever are presenting symptoms of interstitial pneumonitis.<br>ILD presents initially as dyspnea without pulmonary infiltrates and is reported within the first five courses of therapy.<br>Pulmonary infiltrates are diffuse with ground-glass opacities.<br>Pleural effusions occur in 7%–12% of patients and are more common if premedication with corticosteroids is not administered.                                                                                            | Establish baseline pulmonary function and imaging for comparison if respiratory symptoms develop.<br>Withhold pemetrexed for acute onset of new or progressive unexplained pulmonary symptoms, such as dyspnea, cough, or fever, pending diagnostic evaluation. If pneumonitis is confirmed, permanently discontinue pemetrexed.<br>(Adhikari et al., 2016; Breuer & Nechushtan, 2012; Eli Lilly and Company, 2019a; Hochstrasser et al., 2012; Tomii et al., 2017)                                                                                                      |
|                                    | Pentostatin<br>(Nipent™)              | Infection risk, cough<br>Increased risk of fatal pulmonary toxicity when used in combination with fludarabine<br>Acute pulmonary edema in the transplant setting                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Concurrent administration of fludarabine is not recommended due to severe or fatal pulmonary toxicity.<br>(Hospira, 2019)                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Antitumor antibiotics              | Bleomycin sulfate<br>(Blenoxane®)     | Hypersensitivity pneumonitis, pulmonary fibrosis, pulmonary VOD, organizing pneumonia, spontaneous pneumothorax<br>Characteristics of bleomycin-induced pneumonitis include dyspnea and fine rales.                                                                                                                                                                                                                                                                                                                                                                                                                                    | Early toxicity may be self-resolving. Monitor for early warning signs of toxicity to avoid irreversible pulmonary damage.<br>Chest x-rays should be taken every 1–2 weeks. If pulmonary changes are noted, treatment should be discontinued.<br>Increasing toxicity warrants prudently maintaining oxygen levels at room air (25%).<br>(Hospira, 2021b)                                                                                                                                                                                                                  |
|                                    | Mitomycin C<br>(Mitosol®, Mutamycin®) | Bronchospasm, noncardiogenic pulmonary edema, ILD, pulmonary VOD<br>Dyspnea, nonproductive cough, crackles, and capillary leak with progressive respiratory dysfunction indicate ILD.<br>Severe bronchospasm has been reported following administration of vinca alkaloids in patients who previously or simultaneously received mitomycin C. Acute respiratory distress occurring within minutes to hours after the vinca alkaloid injection has been reported. The total doses for each drug has varied considerably.<br>Pulmonary VOD occurs later after exposure (up to 10 years) and leads to symptoms of pulmonary hypertension. | Signs and symptoms of pneumonitis may be reversed if therapy is instituted early.<br>The drug may be discontinued if dyspnea occurs, even with a normal chest x-ray.<br>Caution should be exercised when using oxygen because toxic oxygen injury occurs without other medication-related etiologic precipitators.<br>Pulmonary toxicity with mitomycin can be severe and may be life threatening. Dyspnea with a nonproductive cough and radiographic evidence of pulmonary infiltrates may indicate mitomycin-induced pulmonary toxicity.<br>(Accord Healthcare, 2018) |
|                                    | Mitoxantrone<br>(Novantrone®)         | Hypersensitivity pneumonitis, ILD, organizing pneumonia, sudden-onset dyspnea and tachypnea with hypoxemia, patchy infiltrates on x-ray or computed tomography scan, cough<br>Toxicity usually only occurs when the drug is given with other potentially pulmonary toxic medications.<br>Interstitial pneumonitis has been reported in those receiving mitoxantrone as part of combination chemotherapy.                                                                                                                                                                                                                               | In severe cases, treatment with corticosteroids has produced a rapid response.<br>(Hospira, 2021c; Maldonado et al., 2022b)                                                                                                                                                                                                                                                                                                                                                                                                                                              |

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**TABLE 17-1.** Pulmonary Toxicities of Antineoplastic Agents (*Continued*)

| Classification                     | Drug                                            | Adverse Effects, Signs, and Symptoms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|------------------------------------|-------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Chemotherapy Agents (Cont.)</b> |                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Camptothecins                      | Topotecan (Hycamtin®)                           | Potentially fatal ILD<br>Dyspnea, coughing, and pneumonitis are the main pulmonary side effects.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Establish baseline pulmonary function.<br>Underlying risk factors include a history of ILD, pulmonary fibrosis, lung cancer, thoracic radiation, and the use of pneumotoxic drugs or colony-stimulating factors.<br>Monitor for pulmonary symptoms indicative of ILD. Permanently discontinue topotecan if ILD is confirmed.<br>(Novartis Pharmaceuticals, 2018)                                                                                                                       |
| Differentiating agents             | All-trans retinoic acid (tretinoin; Ves-anoid®) | Retinoic acid differentiation syndrome<br>Pulmonary infiltration of differentiating leukemic cells and their associated chemokines cause inflammatory capillary permeability with sudden and severe hypoxemia.<br>Differentiation syndrome is present with all-trans retinoic acid or arsenic individually or in combination therapies.<br>It occurs in a bimodal pattern, with 46% developing symptoms in the first week of therapy and 36% having symptoms between the third and fourth weeks.<br>Characteristic features of this syndrome include fever, myalgias, arthralgias, weight gain, peripheral edema, respiratory distress with pulmonary infiltrates, hypotension, hepatic and renal dysfunction, rash, and effusions.<br>Pulmonary hemorrhage has occurred in severe cases of differentiation syndrome but may be difficult to differentiate from coagulopathies common in acute promyelocytic leukemia. | Close monitoring of intake and output, weight, vital signs, and breath sounds may assist in early detection.<br>Monitor oxygen saturation for early signs of hypoxemia on exertion.<br>Monitor chest x-ray for pulmonary infiltrates that may precede clinical symptoms.<br>Monitor laboratory values for evidence of renal dysfunction.<br>(Elemam & Abdelmoety, 2013; Larson & Bag, 2022; Nucci et al., 2015; Roche Laboratories, 2020; Sanz & Montesinos, 2014; Villa et al., 2014) |
| Miscellaneous                      | Arsenic trioxide (Trisenox®)                    | Differentiation syndrome<br>Adverse effects usually are not permanent or irreversible and do not require interruption of therapy.<br>Risk increases with a high white blood cell count, a high percentage of blasts, and pre-existing lung disease.<br>Differentiation syndrome with symptoms of fever, hypoxia, dyspnea, ARDS, pulmonary infiltrates, pleural effusion                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Establish baseline pulmonary function.<br>Monitor white blood cell counts and blast percentages.<br>(Larson & Bag, 2022; Leblejian et al., 2013; Sanz & Montesinos, 2014; Teva Pharmaceuticals, 2020)                                                                                                                                                                                                                                                                                  |
| Nitrosoureas                       | Carmustine (BiCNU®)                             | ILD, pulmonary VOD<br>Pulmonary infiltrates and fibrosis can occur from 9 days to 43 months after treatment and appear to be dose related. Fibrosis may be slowly progressive.<br>When carmustine is used in high doses (300–600 mg/m <sup>2</sup> ) prior to hematopoietic stem cell transplantation, pulmonary toxicity may occur and may be dose limiting. The pulmonary toxicity of high-dose carmustine may manifest as severe interstitial pneumonitis, which occurs most frequently in patients who have had recent mediastinal irradiation.<br>A linear relationship exists between total dose and pulmonary toxicity at doses > 1,000 mg/m <sup>2</sup> , with 50% of patients                                                                                                                                                                                                                                | Perform baseline and regular PFTs, especially in patients with risk factors or those who have received > 800 mg/m <sup>2</sup> .<br>(Amneal Pharmaceuticals, 2018; Maldonado et al., 2022a; Versluys & Bresters, 2016)                                                                                                                                                                                                                                                                 |

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**TABLE 17-1.** Pulmonary Toxicities of Antineoplastic Agents (*Continued*)

| Classification                      | Drug                                                            | Adverse Effects, Signs, and Symptoms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|-------------------------------------|-----------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Chemotherapy Agents (Cont.)</b>  |                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Nitrosoureas<br>( <i>Cont.</i> )    | Carmustine<br>(BiCNU)<br>( <i>Cont.</i> )                       | developing pulmonary toxicity at total cumulative doses of 1,500 mg/m <sup>2</sup> . Risk factors include preexisting lung disease, smoking, cyclophosphamide therapy, and recent (within months) thoracic irradiation. Patients with baseline forced vital capacity or diffusing capacity of the lung for carbon monoxide < 70% of the predicted value are at high risk. Delayed toxicity after childhood treatment has increased mortality compared to toxicities from other causes. Other risks for increased pulmonary toxicity with carmustine include a history of lung disease and treatment duration.                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                     | Lomustine<br>(Gleostine®)                                       | ILD, pulmonary fibrosis<br>Pulmonary toxicity onset is characterized by an interval of 6 months or longer from the start of therapy with cumulative doses of lomustine usually > 1,100 mg/m <sup>2</sup> . Delayed-onset pulmonary fibrosis occurring up to 17 years after treatment has been reported in patients who received nitrosoureas in childhood and early adolescence (aged 1–16 years) combined with cranial irradiation for intracranial tumors.                                                                                                                                                                                                                       | Establish baseline pulmonary function.<br>Monitor high-risk patients with PFTs.<br>Permanently discontinue if patient is diagnosed with pulmonary fibrosis.<br>(NextSource Biotechnology, 2018)                                                                                                                                                                                                                                                                                              |
| Plant alkaloids: epipodophylotoxins | Etoposide<br>(Toposar®),<br>etoposide phosphate<br>(Etopophos®) | Bronchospasm, interstitial pneumonitis, pulmonary fibrosis, pulmonary hypertension, pulmonary edema<br>Anaphylactic-like reactions have occurred during the initial infusion of etoposide. Facial or tongue swelling, coughing, diaphoresis, cyanosis, tightness in the throat, laryngospasm, back pain, and loss of consciousness have occurred. An apparent hypersensitivity-associated apnea has been reported rarely.<br>Toxicity is increased with low serum albumin and impaired renal function.<br>Increased methotrexate blood levels occurred when drugs were given concomitantly, but it is unclear whether this is due to etoposide interaction or decreased clearance. | Following bronchospasm, patients have been premedicated and successfully rechallenged with etoposide.<br>Chronic lung disease is difficult to identify, as this agent is usually administered with other pulmonary toxic agents.<br>(Bristol-Myers Squibb, 2019; Maldonado et al., 2022a)                                                                                                                                                                                                    |
| Plant alkaloids: taxanes            | Docetaxel<br>(Taxotere®)                                        | Bronchospasm, hypersensitivity pneumonitis, ILD, pleural effusion, noncardiogenic pulmonary edema                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Pleural effusions may be reversible with diuretics. Pulmonary fibrosis is not consistently responsive to corticosteroids. Hypersensitivity skin testing has been useful in the identification of reactions. Radiation pneumonitis may occur in patients receiving concomitant radiation therapy. The usual steroid dose to prevent pleural effusions is dexamethasone 4–8 mg the day prior to or the same day as docetaxel administration.<br>(Kuo et al., 2015; Sanofi-Aventis U.S., 2021b) |

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**TABLE 17-1.** Pulmonary Toxicities of Antineoplastic Agents (*Continued*)

| Classification                               | Drug                                                                          | Adverse Effects, Signs, and Symptoms                                                                                                                                                                                                                                                                                                                                                                                                            | Nursing Considerations                                                                                                                                                                                                                                                                                                                                 |
|----------------------------------------------|-------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Chemotherapy Agents (Cont.)</b>           |                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                        |
| Plant alkaloids: taxanes<br>( <i>Cont.</i> ) | Paclitaxel                                                                    | Bronchospasm, hypersensitivity pneumonitis, pulmonary fibrosis, radiation recall<br>Rare reports exist of radiation pneumonitis recall phenomenon in patients receiving concurrent radiation.<br>Bronchoalveolar lavage in early lung toxicity showed lymphocytosis in cases of reported hypersensitivity pneumonitis.                                                                                                                          | Toxicity is rarely severe or fatal and often responds to corticosteroids.<br>Incidence may be higher in weekly rather than every-three-week dosing.<br>Incidence is higher when administered with gemcitabine or radiation.<br>(Hospira, 2021b)                                                                                                        |
|                                              | Paclitaxel protein-bound particles; albumin-bound (nab-paclitaxel; Abraxane®) | Risk of pneumonitis when combined with gemcitabine                                                                                                                                                                                                                                                                                                                                                                                              | Hold drug during workup for suspected pneumonitis, and discontinue treatment permanently if diagnosed.<br>Instruct patients to monitor for and report sudden onset of dry, persistent cough, or shortness of breath.<br>(Celgene, 2020a)                                                                                                               |
| Plant alkaloids: vinca alkaloids             | Vinorelbine tartrate (Navelbine®)                                             | Bronchospasm, ILD, ARDS<br>Acute shortness of breath and severe bronchospasm have occurred, most commonly when vinorelbine was used in combination with mitomycin C; these adverse events may require treatment with supplemental oxygen, bronchodilators, or corticosteroids, particularly with preexisting pulmonary complications.<br>The mean time to onset of these symptoms after vinorelbine administration is 1 week (range: 3–8 days). | Patients with alterations in their baseline pulmonary function or new onset of dyspnea, cough, hypoxia, or other symptoms should be evaluated promptly.<br>Hold treatment in the presence of unexplained dyspnea or pulmonary toxicity. Permanently discontinue if confirmed interstitial pneumonitis or ARDS.<br>(Pierre Fabre Pharmaceuticals, 2021) |
| <b>Targeted Agents</b>                       |                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                        |
|                                              | Abemaciclib (Verena®)                                                         | Pneumonitis or ILD presenting with hypoxia, cough, dyspnea, and interstitial infiltrates                                                                                                                                                                                                                                                                                                                                                        | Monitor for signs and symptoms of pneumonitis and ILD. If grade 3–4 pneumonitis or ILD occurs, permanently discontinue the drug.<br>Patient education should include monitoring for shortness of breath, cough, and chest pain.<br>(Eli Lilly and Company, 2021)                                                                                       |
|                                              | Acalabrutinib (Calquence®)                                                    | Upper respiratory tract infection                                                                                                                                                                                                                                                                                                                                                                                                               | Monitor for opportunistic infections, including upper respiratory tract infections.<br>(AstraZeneca Pharmaceuticals, 2019)                                                                                                                                                                                                                             |
|                                              | Afatinib (Gilotrif®)                                                          | Dyspnea, cough, fever, interstitial pneumonitis, respiratory infection, ILD lung infiltrates, ARDS, alveolitis allergic                                                                                                                                                                                                                                                                                                                         | Hold the drug if ILD is suspected, and discontinue if patient is diagnosed with ILD.<br>(Boehringer Ingelheim, 2019)                                                                                                                                                                                                                                   |
|                                              | Alectinib (Alecensa®)                                                         | ILD presents with cough, dyspnea, and fever.                                                                                                                                                                                                                                                                                                                                                                                                    | Hold drug during workup and permanently discontinue if determined to cause ILD or pneumonitis.<br>Instruct patients to report respiratory symptoms immediately.<br>(Genentech, 2021a)                                                                                                                                                                  |

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**TABLE 17-1.** Pulmonary Toxicities of Antineoplastic Agents (*Continued*)

| Classification                 | Drug                                 | Adverse Effects, Signs, and Symptoms                                                                                                                                                                                                                                                                             | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|--------------------------------|--------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Targeted Agents (Cont.)</b> |                                      |                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|                                | Alpelisib (Piqray <sup>®</sup> )     | Pneumonitis, including acute interstitial pneumonitis and ILD<br>May present with hypoxia, cough, dyspnea, and interstitial infiltrates                                                                                                                                                                          | Hold drug during workup and permanently discontinue if determined to cause ILD or pneumonitis.<br>Instruct patients to report respiratory symptoms immediately.<br>Infectious, neoplastic, and other causes should be ruled out.<br>(Novartis Pharmaceuticals, 2022d)                                                                                                                                                                                                                                                                                                                       |
|                                | Binimetinib (Mektovi <sup>®</sup> )  | ILD is a risk. Evaluate pulmonary symptoms that are new, unexplained, or progressive.                                                                                                                                                                                                                            | Hold drug during workup and permanently discontinue if determined to cause ILD or pneumonitis.<br>Instruct patients to report respiratory symptoms immediately.<br>(Array BioPharma, 2020)                                                                                                                                                                                                                                                                                                                                                                                                  |
|                                | Bortezomib (Velcade <sup>®</sup> )   | Pneumonitis; sudden respiratory distress with accompanying pulmonary infiltrates, interstitial pneumonia, ARDS, pulmonary hypertension, and acute diffuse infiltrative pulmonary disease; some of these events have been fatal. Toxicities have inconsistent reversibility or responsiveness to corticosteroids. | Immediate discontinuation of this drug is recommended when pulmonary symptoms occur.<br>(Maldonado et al., 2022a; Takeda Pharmaceuticals, 2021b)                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                | Bosutinib (Bosulif <sup>®</sup> )    | Fluid retention, presenting as pulmonary edema or pleural effusion                                                                                                                                                                                                                                               | Advise patients to report shortness of breath and cough, especially with the presence of fluid retention.<br>(Pfizer, 2021a)                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                | Brigatinib (Alunbrig <sup>®</sup> )  | ILD and pneumonitis usually occur early, within 9 days of initiation of medication. Adverse reactions, such as ILD and pneumonitis, can occur in varying grades of severity.                                                                                                                                     | Unlike similar kinase inhibitors, this drug has the potential for tolerization and continued dosing after pulmonary toxicity. Therefore, it should be initiated at a low dose and increased if tolerated without adverse effects in first 7 days. Monitor for new or worsening respiratory symptoms, such as dyspnea or cough, during the first week of treatment. If new or worsening respiratory symptoms occur, discontinue the drug and evaluate for ILD and pneumonitis. If ILD or pneumonitis is present, follow grade-specific dosage instructions.<br>(Ariad Pharmaceuticals, 2022) |
|                                | Capmatinib (Tabrecta <sup>®</sup> )  | ILD and pneumonitis (potentially fatal)                                                                                                                                                                                                                                                                          | Hold the drug during evaluation and discontinue permanently if ILD or pneumonitis occurs. Monitor for cough, dyspnea, and fever. Instruct patients to notify the healthcare team of respiratory symptoms.<br>(Novartis Pharmaceuticals, 2022e)                                                                                                                                                                                                                                                                                                                                              |
|                                | Carfilzomib (Kyprolis <sup>®</sup> ) | Potentially fatal respiratory events, including pulmonary toxicity (e.g., ARDS, acute respiratory failure, acute diffuse infiltrative pulmonary disease), pulmonary hypertension, and pulmonary hemorrhage                                                                                                       | Instruct patients to notify the healthcare team of respiratory symptoms.<br>(Onyx Pharmaceuticals, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|                                | Ceritinib (Zykadia <sup>®</sup> )    | ILD and pneumonitis (potentially fatal)                                                                                                                                                                                                                                                                          | Discontinue medication for ILD or pneumonitis. Monitor for dyspnea, fever, and cough. Instruct patients to notify the healthcare team of respiratory symptoms.<br>(Novartis Pharmaceuticals, 2022h)                                                                                                                                                                                                                                                                                                                                                                                         |

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**TABLE 17-1.** Pulmonary Toxicities of Antineoplastic Agents (*Continued*)

| Classification                 | Drug                       | Adverse Effects, Signs, and Symptoms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                         |
|--------------------------------|----------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Targeted Agents (Cont.)</b> |                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                |
|                                | Copanlisib<br>(Aliqopa®)   | Noninfectious pneumonitis                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Hold treatment if grade 1–2 adverse events occur. Resume treatment at 45 mg if recovery to grade 0 or 1. Discontinue if noninfectious pneumonitis recurs and is $\geq$ grade 3. Monitor for cough, dyspnea, hypoxia, or interstitial infiltrates on radiologic examination. Instruct patients to report any new or worsening respiratory symptoms.<br>(Bayer HealthCare Pharmaceuticals, 2022) |
|                                | Crizotinib<br>(Xalkori®)   | Dyspnea, ILD, pneumonitis, respiratory tract infections, ARDS, PE<br>ILD presents as dyspnea with pulmonary infiltrates. All cases of ILD presented within the first 2 months of therapy.<br>Reports of dyspnea warrant temporary discontinuation of agent until ILD can be ruled out.                                                                                                                                                                                                                                                                                                      | Coadministration of other pulmonary toxic agents or lung irradiation warrants frequent physical assessment and diagnostic tests, such as imaging or PFTs.<br>If treatment-related ILD is strongly suspected, permanent discontinuation of the drug is recommended.<br>(Kwon & Meagher, 2012; Pfizer, 2021c)                                                                                    |
|                                | Dacomitinib<br>(Vizimpro®) | ILD and pneumonitis are rare but serious and can be fatal, presenting as dyspnea, cough, and fever.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Advise patients to monitor respiratory status and to report new or worsening symptoms, including shortness of breath, cough, or fever. Discontinue the drug permanently if ILD is confirmed.<br>(Pfizer, 2020)                                                                                                                                                                                 |
|                                | Dasatinib<br>(Sprycel®)    | ILD, pleural effusion, pulmonary VOD, pulmonary arterial hypertension (e.g., dyspnea, fatigue, hypoxia, fluid retention), ARDS, PE<br>Most effusions are exudative and characterized by lymphocytic infiltration of the pleura. Lymphocytic effusion is associated with tumor response rates.<br>Most patients who develop grade 3–4 pleural effusions have accelerated- or blast-phase chronic myeloid leukemia.<br>Symptoms include dyspnea, cough, and chest pain.<br>Patients aged $\geq$ 65 years are more likely to experience pleural effusion, dyspnea, cough, and pulmonary edema. | Treatment may include interruption of medication and administration of diuretics or corticosteroids. Dose reduction may also be recommended.<br>(Bristol-Myers Squibb, 2021)                                                                                                                                                                                                                   |
|                                | Duvelisib<br>(Copiktra®)   | Serious and potentially fatal noninfectious pneumonitis cases are diagnosed between 4–9 months after treatment initiation and last for 1–2 months. Symptoms include cough, dyspnea, hypoxia, and interstitial infiltrates seen on radiology examination or decline in oxygen saturation of $> 5\%$ .                                                                                                                                                                                                                                                                                        | Hold the drug when grade 2 noninfectious pneumonitis occurs, and treat with corticosteroids. Resume at a reduced dose after resolution. If no response or recurrence, discontinue the drug.<br>Treat with systemic steroids and discontinue for severe or life-threatening pneumonitis. Educate patients to report new or worsening respiratory symptoms.<br>(Secura Bio, 2021)                |
|                                | Enasidenib<br>(Idhifa®)    | Acute respiratory distress, pulmonary infiltrates, pleural effusions, differentiation syndrome                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Monitor for signs of differentiation syndrome and symptoms of dyspnea, pleural effusion, and pulmonary edema.<br>(Celgene, 2020b)                                                                                                                                                                                                                                                              |

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**TABLE 17-1.** Pulmonary Toxicities of Antineoplastic Agents (*Continued*)

| Classification                 | Drug                                                                  | Adverse Effects, Signs, and Symptoms                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                    |
|--------------------------------|-----------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Targeted Agents (Cont.)</b> |                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                                | Erlotinib (Tarceva®)                                                  | ILD, pulmonary fibrosis, organizing pneumonia, radiation recall pneumonitis<br>Fatal ILD has been associated with oral erlotinib therapy for lung cancer.<br>Toxicities can occur days to months after exposure.                                                                                                                                                                                                                                                                      | Some patients have shown clinical improvement with corticosteroid treatment.<br>Strong suspicion of erlotinib-induced lung injury warrants discontinuation of the drug.<br>Hold the drug for pulmonary symptoms such as dyspnea, cough, and fever that are new or progressive. Permanently discontinue if ILD is confirmed.<br>(Armas Pharmaceuticals, 2019; Awad & Nott, 2016; Maldonado et al., 2022b; Qi et al., 2015) |
|                                | Everolimus (Afinitor®; Afinitor Disperz® tablets for oral suspension) | Cough, dyspnea, ILD, hypersensitivity pneumonitis, diffuse alveolar hemorrhage, organizing pneumonia, pleural effusion, pulmonary hypertension, pulmonary fibrosis                                                                                                                                                                                                                                                                                                                    | Acute onset of respiratory distress warrants immediate discontinuation of the drug with diagnostic testing. Treatment with corticosteroids may be indicated.<br>(Nishino et al., 2016; Novartis Pharmaceuticals, 2021a; Willemssen et al., 2016)                                                                                                                                                                          |
|                                | Gefitinib (Iressa®)                                                   | ILD, diffuse alveolar hemorrhage, pulmonary fibrosis, ARDS, organizing pneumonia<br>Patients often present with acute-onset dyspnea, sometimes associated with cough or low-grade fever, that often quickly becomes severe and requires hospitalization.<br>Increased mortality has been observed in patients with concurrent idiopathic pulmonary fibrosis whose condition worsens while receiving the drug.<br>Alveolar hemorrhage presents within 24–42 days after administration. | If acute onset or worsening of pulmonary symptoms (e.g., dyspnea, cough, fever) occurs, therapy should be interrupted and symptoms promptly investigated. If ILD is confirmed, discontinue the drug.<br>(AstraZeneca Pharmaceuticals, 2021; Qi et al., 2015)                                                                                                                                                              |
|                                | Gilteritinib (Xospata®)                                               | Differentiation syndrome may include symptoms of dyspnea, pleural effusion, and pulmonary edema.                                                                                                                                                                                                                                                                                                                                                                                      | Treat differentiation syndrome with corticosteroids. Hold the drug until symptoms are no longer severe.<br>(Astellas Pharmaceuticals, 2022)                                                                                                                                                                                                                                                                               |
|                                | Idelalisib (Zydelig)                                                  | Monitor for cough, dyspnea, hypoxia, and interstitial infiltrates, or an oxygen saturation decrease of 5% or more.                                                                                                                                                                                                                                                                                                                                                                    | Discontinue the drug if pneumonitis occurs, and treat with corticosteroids.<br>(Gilead Sciences, 2022)                                                                                                                                                                                                                                                                                                                    |
|                                | Imatinib mesylate (Gleevec®)                                          | Dyspnea of uncertain significance, hypersensitivity pneumonitis, noncardiogenic pulmonary edema, ILD, pulmonary alveolar proteinosis, pleural effusions<br>Fluid retention events include pleural effusion, ascites, pulmonary edema, pericardial effusion, and anasarca.<br>Fluid extravasation and pleural effusions appear to be dose related, were more common in the blast crisis and accelerated-phase studies (600 mg daily dose), and were more common in older adults.       | Weigh and monitor patients regularly for signs and symptoms of fluid retention.<br>Investigate unexpected rapid weight gain carefully and provide appropriate treatment.<br>These events are usually managed by interrupting treatment and using diuretics or other appropriate supportive care measures. Symptoms often resurface when rechallenging with this drug.<br>(Mylan Pharmaceuticals, 2022)                    |
|                                | Ivosidenib (Tibsovo®)                                                 | Differentiation syndrome may include symptoms of dyspnea, pleural effusion, and pulmonary edema.                                                                                                                                                                                                                                                                                                                                                                                      | Treat differentiation syndrome with corticosteroids. Hold the drug until symptoms are no longer severe.<br>(Servier Pharmaceuticals, 2022)                                                                                                                                                                                                                                                                                |

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**TABLE 17-1.** Pulmonary Toxicities of Antineoplastic Agents (*Continued*)

| Classification                 | Drug                     | Adverse Effects, Signs, and Symptoms                                                                                                     | Nursing Considerations                                                                                                                                                                                                                                       |
|--------------------------------|--------------------------|------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Targeted Agents (Cont.)</b> |                          |                                                                                                                                          |                                                                                                                                                                                                                                                              |
|                                | Lapatinib (Tykerb®)      | ILD and pneumonitis                                                                                                                      | Monitor for cough and dyspnea. Discontinue the drug in patients with $\geq$ grade 3 ILD or pneumonitis. (Novartis Pharmaceuticals, 2022f)                                                                                                                    |
|                                | Lorlatinib (Lorbrena®)   | ILD and pneumonitis                                                                                                                      | Hold the drug in patients with suspected ILD or pneumonitis. Permanently discontinue with ILD or pneumonitis of any severity. (Pfizer, 2021b)                                                                                                                |
|                                | Midostaurin (Rydapt®)    | Pulmonary complications include upper respiratory tract infection, dyspnea, and ILD and pneumonitis.                                     | Monitor for symptoms of pulmonary complications. Discontinue if noninfectious ILD or pneumonitis occurs. Advise patients to monitor for and report cough, chest discomfort, or dyspnea. (Novartis Pharmaceuticals, 2021c)                                    |
|                                | Mobocertinib (Exkivity®) | ILD and pneumonitis (potentially fatal)                                                                                                  | Hold the drug for suspected ILD or pneumonitis. Discontinue if confirmed. Advise patients to report cough, dyspnea, or chest pain. (Takeda Pharmaceuticals, 2021a)                                                                                           |
|                                | Olaparib (Lynparza®)     | Pneumonitis (potentially fatal), cough, dyspnea, fever, radiologic abnormalities, respiratory tract infections                           | Hold the drug for suspected ILD or pneumonitis. Discontinue if confirmed. Advise patients to report shortness of breath, fever, cough, or wheezing. (AstraZeneca Pharmaceuticals, 2022b)                                                                     |
|                                | Osimertinib (Tagrisso®)  | ILD or pneumonitis (potentially fatal), presenting as cough, dyspnea, fever                                                              | Discontinue permanently with the presence of ILD or pneumonitis. Advise patients to report cough, dyspnea, or fever. (AstraZeneca Pharmaceuticals, 2022c)                                                                                                    |
|                                | Palbociclib (Ibrance®)   | ILD or pneumonitis (severe and potentially fatal) when administered concurrently with endocrine therapy                                  | Hold the drug to evaluate respiratory symptoms. Permanently discontinue the drug with the presence of ILD or pneumonitis. Advise patients to report cough, dyspnea, or hypoxia. (Pfizer, 2019)                                                               |
|                                | Pazopanib (Votrient®)    | Pneumothorax may present as dyspnea, chest pain, and localized limb edema. ILD and pneumonitis present with cough, dyspnea, and hypoxia. | Permanently discontinue the drug with the presence of ILD or pneumonitis. Advise patients to report persistent cough and dyspnea. (Novartis Pharmaceuticals, 2022g)                                                                                          |
|                                | Pralsetinib (Gavreto®)   | ILD and pneumonitis (potentially fatal)                                                                                                  | Hold the drug with grade 1–2 pneumonitis. Resume at a reduced dose after resolution. Discontinue the drug for severe or life-threatening grade 3–4 pneumonitis. Advise patients to monitor for and report worsening respiratory symptoms. (Genentech, 2022a) |

(Continued on next page)

**TABLE 17-1.** Pulmonary Toxicities of Antineoplastic Agents (*Continued*)

| Classification                 | Drug                                 | Adverse Effects, Signs, and Symptoms                                                                                                                                                                                                                                     | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|--------------------------------|--------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Targeted Agents (Cont.)</b> |                                      |                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|                                | Ribociclib (Kisqali <sup>®</sup> )   | ILD and pneumonitis (severe and potentially fatal)                                                                                                                                                                                                                       | Do not interrupt treatment if ILD or pneumonitis is grade 1.<br>Hold the drug and treat grade 2 ILD or pneumonitis. Resume at reduced dose after resolution.<br>Discontinue if grade 2 recurs or for severe or life-threatening, grade 3–4 pneumonitis.<br>Advise patients to monitor for and report worsening respiratory symptoms (Novartis Pharmaceuticals, 2022a)                                                                                                                                                                                                                                                                                                         |
|                                | Sorafenib (Nexavar <sup>®</sup> )    | Dyspnea<br>In postmarketing experience, ILD-like events were reported with potential life-threatening or fatal outcomes, including reports of pneumonitis, radiation pneumonitis, acute respiratory distress, interstitial pneumonia, pulmonitis, and lung inflammation. | (Bayer HealthCare Pharmaceuticals, 2020)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|                                | Sotorasib (Lumakras <sup>®</sup> )   | ILD and pneumonitis (potentially fatal), occurring between 2 and 18 weeks<br>Cough, respiratory failure, pneumonia, dyspnea, upper airway cough syndrome                                                                                                                 | Advise patients to promptly report any new or worsening respiratory symptoms.<br>Hold the drug if ILD or pneumonitis are suspected, and permanently discontinue if confirmed at any grade.<br>(Amgen, 2021a)                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|                                | Temsirolimus (Torisel <sup>®</sup> ) | <i>Pneumocystis jirovecii</i> pneumonia, leading to fatalities<br>ILD, hypoxia, dyspnea, cough, pneumonia, upper respiratory infection, PE                                                                                                                               | Advise patients to promptly report any new or worsening respiratory symptoms.<br>Patients should undergo baseline radiographic assessment by lung computed tomography scan or chest x-ray prior to the initiation of therapy and periodically thereafter, even in the absence of clinical respiratory symptoms.<br>Monitor for symptoms or radiographic changes of ILD. If ILD is suspected, discontinue the drug and consider use of corticosteroids and antibiotics.<br>Prophylaxis of <i>Pneumocystis jirovecii</i> pneumonia should be considered when concomitant use of corticosteroids or other immunosuppressive agents is required.<br>(Wyeth Pharmaceuticals, 2022) |
|                                | Tepotinib (Tepmetko <sup>®</sup> )   | Pneumonia, pleural effusion, PE<br>ILD and pneumonitis presenting with pulmonary symptoms of dyspnea, cough (may be productive), fever                                                                                                                                   | Advise patients to promptly report any new or worsening respiratory symptoms.<br>Hold the drug if ILD or pneumonitis is suspected, and permanently discontinue if confirmed at any grade.<br>(EMD Serono, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|                                | Trametinib (Mekinist <sup>®</sup> )  | Symptoms of ILD and pneumonitis, including dyspnea, hypoxia, cough, pleural effusion, infiltrates<br>PE, pulmonary hemorrhage<br>Respiratory distress is a common reason for medication discontinuation.                                                                 | Hold the drug for pulmonary symptoms and evaluate for potential ILD. Discontinue the drug if ILD is confirmed.<br>Advise patients to immediately seek medical care if they develop symptoms of deep vein thrombosis or PEs, such as shortness of breath, chest pain, or arm or leg swelling.                                                                                                                                                                                                                                                                                                                                                                                  |

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**TABLE 17-1.** Pulmonary Toxicities of Antineoplastic Agents (*Continued*)

| Classification                                          | Drug                                 | Adverse Effects, Signs, and Symptoms                                                                                                                                                                                                                                                                                                                                                                                                                            | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|---------------------------------------------------------|--------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Targeted Agents (Cont.)</b>                          |                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                         | Trametinib<br>(Mekinist®)<br>(Cont.) |                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | For uncomplicated PE, withhold the drug for up to 3 weeks. If symptoms improve to grade 0–1, resume the drug at a lower dose. If symptoms do not improve, permanently discontinue the drug.<br>For life-threatening PE, permanently discontinue the drug.<br>(Novartis Pharmaceuticals, 2022c)                                                                                                                                                                                                                                                                                                                                                                                          |
|                                                         | Vandetanib<br>(Caprelsa®)            | Upper respiratory infection, signs of ILD or pneumonitis                                                                                                                                                                                                                                                                                                                                                                                                        | Hold the drug during evaluation for nonspecific respiratory symptoms. Discontinue the drug if ILD or pneumonitis is confirmed. Advise patients to report sudden onset or worsening of breathlessness, persistent cough, or fever.<br>(Genzyme, 2022)                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <b>Immunotherapy Agents</b>                             |                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Checkpoint inhibitors: cytotoxic T-lymphocyte antigen 4 | Ipilimumab<br>(Yervoy®)              | Infusion reactions, immune-mediated pneumonitis, cough (may be productive), dyspnea, upper respiratory infection, PE, upper airway cough syndrome, pneumonia (e.g., lower respiratory tract infection, lung infection, aspiration pneumonia, <i>Pneumocystis jirovecii</i> pneumonia)                                                                                                                                                                           | Advise patients to immediately report any new or worsening cough, chest pain, or shortness of breath due to concern for the development of pneumonitis or any signs or symptoms of an infusion reaction.<br>For grade 2 pneumonitis, withhold treatment. For grade 3–4 pneumonitis, permanently discontinue treatment.<br>For grade 1–2 infusion-related reactions, interrupt or slow the rate of infusion.<br>For grade 3–4 infusion-related reactions, permanently discontinue treatment.<br>Steroids may be required to treat pneumonitis symptoms.<br>See MASCC guidelines for the treatment of immune-mediated pneumonitis.<br>(Bristol-Myers Squibb, 2022c; Shannon et al., 2020) |
| Checkpoint inhibitors: programmed cell death-ligand 1   | Atezolizumab<br>(Tecentriq®)         | Immune-related adverse reactions, including pneumonitis<br>Cough (may be productive), dyspnea, infusion reactions, ILD, pneumothorax, respiratory infection, upper respiratory infection, wheezing, pleural effusion, bronchitis<br>The incidence of pneumonitis is higher in patients who have received prior thoracic irradiation.<br>Fatal reactions include aspiration, COPD, PE, pulmonary hemorrhage, respiratory distress, and cardiorespiratory arrest. | Advise patients to immediately report any new or worsening cough, chest pain, or shortness of breath, due to concern for the development of pneumonitis or any signs or symptoms of an infusion reaction.<br>For grade 2 pneumonitis, withhold treatment. For grade 3–4 pneumonitis, permanently discontinue treatment.<br>For grade 1–2 infusion-related reactions, interrupt or slow the rate of infusion.<br>For grade 3–4 infusion-related reactions, permanently discontinue treatment.<br>Steroids may be required to treat pneumonitis symptoms.<br>See MASCC guidelines for the treatment of immune-mediated pneumonitis.<br>(Genentech, 2021d; Shannon et al., 2020)           |

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**TABLE 17-1.** Pulmonary Toxicities of Antineoplastic Agents (*Continued*)

| Classification                                                         | Drug                       | Adverse Effects, Signs, and Symptoms                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|------------------------------------------------------------------------|----------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Immunotherapy Agents (Cont.)</b>                                    |                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Checkpoint inhibitors: programmed cell death-ligand 1 ( <i>Cont.</i> ) | Avelumab (Bavencio®)       | Immune-related adverse reactions, including pneumonitis (potentially fatal with respiratory failure)<br>Cough (may be productive), dyspnea, pneumonia, infusion-related reactions<br>The incidence of pneumonitis is higher in patients who have received prior thoracic radiation.                                                                                                                                                                                                        | Premedicate with antihistamine and acetaminophen prior to the first 4 infusions. Monitor patients for signs and symptoms of infusion-related reactions, including dyspnea and wheezing.<br>Advise patients to immediately report any new or worsening cough, chest pain, or shortness of breath due to concern for the development of pneumonitis or any signs or symptoms of an infusion reaction.<br>For grade 2 pneumonitis, withhold treatment. For grade 3–4 pneumonitis, permanently discontinue treatment.<br>For grade 1–2 infusion-related reactions, interrupt or slow the rate of infusion. For grade 3–4 infusion-related reactions, permanently discontinue treatment. Steroids may be required to treat pneumonitis symptoms.<br>See MASCC guidelines for the treatment of immune-mediated pneumonitis. (EMD Serono, 2022; Shannon et al., 2020) |
|                                                                        | Durvalumab (Imfinzi®)      | Pneumonitis/radiation pneumonitis, upper respiratory tract infections, dyspnea, pneumonia, cough<br>The incidence of pneumonitis is higher in patients who have received prior thoracic radiation.                                                                                                                                                                                                                                                                                         | Advise patients to immediately report any new or worsening cough, chest pain, or shortness of breath due to concern for the development of pneumonitis or any signs or symptoms of an infusion reaction.<br>For grade 2 pneumonitis, withhold treatment. For grade 3–4 pneumonitis, permanently discontinue treatment.<br>For grade 1–2 infusion-related reactions, interrupt or slow the rate of infusion. For grade 3–4 infusion-related reactions, permanently discontinue treatment. Steroids may be required to treat pneumonitis symptoms.<br>See MASCC guidelines for the treatment of immune-mediated pneumonitis. (AstraZeneca Pharmaceuticals, 2022a; Shannon et al., 2020)                                                                                                                                                                          |
| Checkpoint inhibitors: programmed cell death protein 1                 | Cemiplimab-rwlc (Libtayo®) | Potential for serious immune-related toxicities, including pneumonitis<br>Presentation with cough (upper airway cough syndrome), dyspnea, hypoxia, chest pain, pneumonia (e.g., atypical pneumonia, embolic pneumonia, lower respiratory tract infection, lung abscess, paraneoplastic pneumonia, bacterial pneumonia, <i>Klebsiella pneumoniae</i> ), upper respiratory tract infection<br>The incidence of pneumonitis is higher in patients who have received prior thoracic radiation. | Advise patients to immediately report any new or worsening cough, chest pain, or shortness of breath due to concern for the development of pneumonitis or any signs or symptoms of an infusion reaction.<br>For grade 2 pneumonitis, withhold treatment. For grade 3–4 pneumonitis, permanently discontinue treatment.<br>For grade 1–2 infusion-related reactions, interrupt or slow the rate of infusion. For grade 3–4 infusion-related reactions, permanently discontinue treatment. Steroids may be required to treat pneumonitis symptoms.<br>Pneumonitis and pneumonia have led to the permanent discontinuation of medication. See MASCC guidelines for the treatment of immune-mediated pneumonitis. (Regeneron, 2021; Shannon et al., 2020)                                                                                                          |

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**TABLE 17-1.** Pulmonary Toxicities of Antineoplastic Agents (*Continued*)

| Classification                                                          | Drug                         | Adverse Effects, Signs, and Symptoms                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|-------------------------------------------------------------------------|------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Immunotherapy Agents (Cont.)</b>                                     |                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Checkpoint inhibitors: programmed cell death protein 1 ( <i>Cont.</i> ) | Dostarlimab-gxly (Jemperli®) | Potential for serious immune-related toxicities, including pneumonitis<br>Presentation with cough, dyspnea, hypoxia, bronchitis, ILD<br>The incidence of pneumonitis is higher in patients who have received prior thoracic radiation.                                                                                                                                                                                                                                                    | Advise patients to immediately report any new or worsening cough, chest pain, or shortness of breath due to concern for the development of pneumonitis or any signs or symptoms of an infusion reaction.<br>For grade 2 pneumonitis, withhold treatment.<br>For grade 3–4 pneumonitis, permanently discontinue treatment.<br>For grade 1–2 infusion-related reactions, interrupt or slow the rate of infusion.<br>For grade 3–4 infusion-related reactions, permanently discontinue treatment.<br>Steroids may be required to treat pneumonitis symptoms.<br>See MASCC guidelines for the treatment of immune-mediated pneumonitis.<br>(GlaxoSmithKline, 2022; Shannon et al., 2020)       |
|                                                                         | Nivolumab (Opdivo®)          | Cough, upper respiratory infection, dyspnea, infusion reactions, interstitial pneumonitis, PE, pneumonia (e.g., lower respiratory tract infection [bacterial], lung infection, pneumonia, adenovirus pneumonia, aspiration pneumonia, bacterial pneumonia, <i>Klebsiella pneumoniae</i> , influenzal pneumonia, viral pneumonia, atypical pneumonia, organizing pneumonia)<br>The incidence of pneumonitis is higher in patients who have received prior thoracic irradiation.            | Advise patients to immediately report any new or worsening cough, chest pain, or shortness of breath due to concern for the development of pneumonitis or any signs or symptoms of an infusion reaction.<br>For grade 2 pneumonitis, withhold treatment.<br>For grade 3–4 pneumonitis, permanently discontinue treatment.<br>For grade 1–2 infusion-related reactions, interrupt or slow the rate of infusion.<br>For grade 3–4 infusion-related reactions, permanently discontinue treatment.<br>Steroids may be required to treat pneumonitis symptoms.<br>See MASCC guidelines for the treatment of immune-mediated pneumonitis.<br>(Bristol-Myers Squibb, 2022b; Shannon et al., 2020) |
|                                                                         | Pembrolizumab (Keytruda®)    | Cough (may be productive), dyspnea, infusion reactions (e.g., wheezing, hypoxemia), interstitial pneumonitis, upper respiratory tract infection, PE, pleural effusion, pneumonia (e.g., atypical pneumonia, bacterial pneumonia, <i>Staphylococcus</i> pneumonia, aspiration pneumonia, lower respiratory tract infection, lung infection, pseudomonal lung infection), respiratory failure<br>Pneumonitis rates have been similar in patients with and without prior thoracic radiation. | Advise patients to immediately report any new or worsening cough, chest pain, or shortness of breath due to concern for the development of pneumonitis or any signs or symptoms of an infusion reaction.<br>For grade 2 pneumonitis, withhold treatment.<br>For grade 3–4 pneumonitis, permanently discontinue treatment.<br>For grade 1–2 infusion-related reactions, interrupt or slow the rate of infusion.<br>For grade 3–4 infusion-related reactions, permanently discontinue treatment.<br>Steroids may be required to treat pneumonitis symptoms.<br>See MASCC guidelines for the treatment of immune-mediated pneumonitis.<br>(Merck, 2022a; Shannon et al., 2020)                |

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**TABLE 17-1.** Pulmonary Toxicities of Antineoplastic Agents (*Continued*)

| Classification                      | Drug                                                       | Adverse Effects, Signs, and Symptoms                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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| <b>Immunotherapy Agents (Cont.)</b> |                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Cytokines:<br>interferons           | Interferon<br>alfa-2b<br>(Intron-A <sup>®</sup> )          | Dyspnea, cough, pulmonary infiltrates, pneumonia, bronchiolitis obliterans, interstitial pneumonitis, pulmonary hypertension, sarcoidosis (some resulting in respiratory failure or death; may be induced or aggravated by the medication)<br>Recurrence of respiratory failure has been observed with medication rechallenge.<br>Severe acute hypersensitivity reactions (e.g., bronchoconstriction) have been observed.<br>Postmarketing studies have shown pulmonary hypertension and pulmonary fibrosis. | Use with caution in patients with a history of pulmonary disease (e.g., COPD) or coagulation disorders (e.g., PE).<br>Patients developing fever, cough, dyspnea, or other respiratory symptoms should undergo a chest x-ray. If the chest x-ray shows pulmonary infiltrates or evidence of pulmonary function impairment, patients should be closely monitored, and, if appropriate, treatment should be discontinued.<br>If an acute hypersensitivity reaction develops, the drug should be discontinued immediately and appropriate medical therapy instituted.<br>Baseline chest x-rays are suggested and should be repeated if clinically indicated. (Merck, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                     | Interferon<br>gamma<br>(Actimmune <sup>®</sup> )           | Tachypnea, bronchospasm, pulmonary edema, interstitial pneumonitis                                                                                                                                                                                                                                                                                                                                                                                                                                           | (Horizon Therapeutics, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Cytokines:<br>interleukins          | Aldesleukin<br>(interleukin-2;<br>Proleukin <sup>®</sup> ) | Capillary leak syndrome, causing respiratory failure and leading to intubation<br>Dyspnea, cough, lung disorder (including physical findings associated with pulmonary congestion, rales, and rhonchi), respiratory disorders (e.g., ARDS, chest x-ray infiltrates, unspecified pulmonary changes), pneumonia                                                                                                                                                                                                | The drug should be administered in a hospital setting under the supervision of a qualified physician experienced in anticancer agents. An intensive care facility and specialists skilled in cardiopulmonary or intensive care medicine must be available.<br>Establish baseline pulmonary function with PFTs prior to therapy initiation. Adequate pulmonary function should be documented (forced expiratory volume > 2 L or ≥ 75% of predicted for height and age).<br>During treatment, pulmonary function should be monitored regularly by clinical examination, assessment of vital signs, and pulse oximetry. Patients with dyspnea or clinical signs of respiratory impairment (e.g., tachypnea, rales) should be further assessed with arterial blood gas determination. These tests are to be repeated as often as clinically indicated.<br>The drug is contraindicated in patients with abnormal PFTs.<br>Capillary leak syndrome should be medically managed.<br>Retreatment with medication is contraindicated in patients requiring respiratory intubation for > 72 hours.<br>Withhold the drug when oxygen saturation is < 90%. The drug dose can be resumed when oxygen saturation is > 90%. (Clinigen, 2021) |

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**TABLE 17-1.** Pulmonary Toxicities of Antineoplastic Agents (Continued)

| Classification                      | Drug                     | Adverse Effects, Signs, and Symptoms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|-------------------------------------|--------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Immunotherapy Agents (Cont.)</b> |                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Immunomodulators                    | Lenalidomide (Revlimid®) | PE, dyspnea, upper respiratory tract infection, bronchitis, cough, pneumonia, influenza, lower respiratory tract infection, respiratory distress, COPD, respiratory failure, ILD, lung infiltration, wheezing, pleural effusion, hypoxia<br>Pneumonia seen with medication includes lobar pneumonia, <i>Streptococcus pneumoniae</i> , bronchopneumonia, <i>Pneumocystis jirovecii</i> pneumonia, <i>Legionella pneumoniae</i> , <i>Staphylococcus pneumoniae</i> , <i>Klebsiella pneumoniae</i> , atypical pneumonia, bacterial pneumonia, <i>Escherichia pneumoniae</i> , and viral pneumonia. | When combined with dexamethasone, this drug significantly increases the risk of deep vein thrombosis, PE, myocardial infarction, and stroke in patients with multiple myeloma. Anti-thrombotic prophylaxis is recommended.<br>Advise patients to seek immediate medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling.<br>Erythropoietic agents, or other agents that may increase the risk of thrombosis, such as estrogen-containing therapies, should be used with caution after making a risk-benefit assessment in patients receiving this drug.<br>(Celgene, 2022)                                                                                                  |
|                                     | Pomalidomide (Pomalyst®) | PE, dyspnea, upper respiratory tract infection, pneumonia, cough (can be productive), COPD, ILD, respiratory failure, bronchospasm<br>Pulmonary infections reported include <i>Pneumocystis jirovecii</i> pneumonia, respiratory syncytial virus infection, <i>Streptococcus pneumoniae</i> , lobar pneumonia, viral infection, and lung infection.                                                                                                                                                                                                                                              | Deep venous thrombosis, PE, myocardial infarction, and stroke occur in patients with multiple myeloma treated with this drug. Antithrombotic prophylaxis is recommended.<br>Patients with known risk factors for developing deep vein thrombosis, including prior thrombosis, may be at greater risk. Actions should be taken to minimize all modifiable factors (e.g., hyperlipidemia, hypertension, smoking). Thromboprophylaxis is recommended, and the choice of regimen should be based on the assessment of underlying risk factors.<br>Cigarette smoking reduces drug area under the curve due to CYP1A2 induction.<br>Advise patients that smoking may reduce the efficacy of the medication.<br>(Celgene, 2021a) |
|                                     | Thalidomide (Thalomid®)  | PE, dyspnea, pneumonia, bronchopneumonia, bronchitis<br>Pulmonary side effects seen in uncontrolled studies included cough, emphysema, epistaxis, PE, rales, upper respiratory infection, and voice alteration.<br>Pulmonary side effects seen in HIV-positive patients in uncontrolled studies include apnea, bronchitis, lung disorder, lung edema, pneumonia (e.g., <i>Pneumocystis jirovecii</i> pneumonia), and rhinitis.<br>In postmarketing studies, side effects included pleural effusion and ILD.                                                                                      | The risk of PE development increases when the drug is combined with standard chemotherapy agents, including dexamethasone.<br>Advise patients to seek immediate medical care if they develop symptoms of thromboembolism, such as shortness of breath, chest pain, or arm or leg swelling.<br>Use caution with this medication with erythropoietic agents or other agents that may increase the risk of thromboembolism, such as estrogen-containing therapies.<br>Inform patients of the potential risk of developing venous thromboembolism (e.g., deep vein thrombosis, PE).<br>(Celgene, 2021b)                                                                                                                       |

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**TABLE 17-1.** Pulmonary Toxicities of Antineoplastic Agents (*Continued*)

| Classification                      | Drug                                                                 | Adverse Effects, Signs, and Symptoms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|-------------------------------------|----------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Immunotherapy Agents (Cont.)</b> |                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Monoclonal antibodies: chimeric     | Brentuximab vedotin (anti-CD20 antibody; Adcetris®)                  | Upper respiratory tract infection, pneumonitis, pneumonia, cough, ILD, ARDS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Monitor patients for signs and symptoms of pulmonary toxicity, including cough and dyspnea.<br>If new or worsening pulmonary symptoms occur, hold the drug during evaluation until symptomatic improvement.<br>Concomitant use with bleomycin is contraindicated because of pulmonary toxicity. (Seagen, 2022)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                                     | Cetuximab (anti-epidermal growth factor receptor antibody; Erbitux®) | Dyspnea, cough, ILD (a fatality occurred in a clinical trial)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Premedicate with an H <sub>1</sub> receptor antagonist to decrease the risk of an infusion reaction.<br>For acute or worsening pulmonary symptoms, delay infusion 1–2 weeks; if the condition improves, continue at the dose being administered at the time of occurrence. If no improvement in 2 weeks or ILD is confirmed, discontinue the drug.<br>Advise patients to contact their healthcare provider immediately for new or worsening cough, chest pain, shortness of breath, and signs and symptoms of infusion reactions. (ImClone, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                     | Isatuximab-irfc (Sarclisa®)                                          | Pneumonia, upper respiratory tract infection, bronchitis, cough (may be productive or allergic cough), dyspnea<br>The most common symptoms of an infusion-related reaction are dyspnea and cough.<br>Upper respiratory tract infections include acute sinusitis, chronic sinusitis, H1N1 influenza, H3N2 influenza, influenza, laryngitis, viral laryngitis, nasal herpes, nasopharyngitis, pharyngitis, pharyngotonsillitis, respiratory syncytial virus infection, rhinitis, bacterial sinusitis, tonsillitis, tracheitis, viral rhinitis, viral respiratory tract infection, and influenza-like illness.<br>Examples of pneumonia include atypical pneumonia, viral lower respiratory tract infection, <i>Pneumocystis jirovecii</i> pneumonia, influenzal pneumonia, <i>Legionella</i> pneumonia, <i>Streptococcus</i> pneumonia, respiratory syncytial virus, viral pneumonia, pulmonary sepsis, and pulmonary tuberculosis.<br>Bronchitis examples include viral bronchitis, respiratory syncytial virus bronchitis, chronic bronchitis, and tracheobronchitis. | Infusion-related reactions, including life-threatening anaphylactic reactions, have occurred. Severe signs and symptoms include bronchospasm and dyspnea.<br>To decrease the risk and severity of infusion-related reactions, premedicate patients with acetaminophen, H <sub>2</sub> antagonists, diphenhydramine or equivalent, and dexamethasone.<br>For patients with ≥ grade 2 reactions, interrupt the infusion and provide appropriate medical management. If symptoms improve to ≤ grade, restart infusion at half of the initial infusion rate, with supportive care as needed, and closely monitor patients.<br>If symptoms do not recur after 30 minutes, the infusion rate may be increased to the initial rate and then increased incrementally.<br>If symptoms do not improve after treatment interruption, persist or worsen despite appropriate medications, or require hospitalization, permanently discontinue the drug and institute appropriate management. If an anaphylactic or life-threatening (grade 4) infusion reaction occurs, permanently discontinue the drug.<br>Advise patients to contact their healthcare provider immediately for shortness of breath, wheezing, cough, trouble breathing, and signs and symptoms of infusion reactions. (Sanofi-Aventis U.S., 2021a) |

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**TABLE 17-1.** Pulmonary Toxicities of Antineoplastic Agents (*Continued*)

| Classification                                   | Drug                                                             | Adverse Effects, Signs, and Symptoms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|--------------------------------------------------|------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Immunotherapy Agents (Cont.)</b>              |                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Monoclonal antibodies: chimeric ( <i>Cont.</i> ) | Rituximab (anti-CD20 antibody; Rituxan <sup>®</sup> )            | Cough, bronchospasm, dyspnea<br>Infusion-related symptoms include pulmonary effects, hypoxia, bronchospasm, dyspnea, pulmonary infiltrates, and ARDS.                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Premedicate patients with an antihistamine and acetaminophen prior to dosing to prevent infusion-related reaction.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|                                                  | Rituximab-abbs (Truxima <sup>®</sup> ; biosimilar to rituximab)  | Patients older than 60 years receiving R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) had a higher risk of pulmonary toxicities                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | If an infusion reaction occurs, stop the infusion and institute medical management (e.g., glucocorticoids, epinephrine, bronchodilators, oxygen) as needed. Depending on the severity of the infusion-related reaction and the required interventions, temporarily or permanently discontinue the drug.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|                                                  | Rituximab-arxx (Riabni <sup>™</sup> ; biosimilar to rituximab)   | Postmarketing studies identified fatal bronchiolitis obliterans and fatal ILD.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Resume infusion at a minimum 50% reduction in rate after symptoms have resolved.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|                                                  | Rituximab-pvvr (Ruxience <sup>®</sup> ; biosimilar to rituximab) |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Closely monitor patients with preexisting cardiac or pulmonary conditions, those who experienced prior cardiopulmonary adverse reactions, and those with high numbers of circulating malignant cells ( $\geq 25,000/\text{mm}^3$ ) for infusion-related reactions.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|                                                  | Rituximab and hyaluronidase (Rituxan Hycela <sup>®</sup> )       | Dyspnea, upper respiratory infection, pneumonia, bronchitis, cough, hypersensitivity reaction<br>Severe cytokine release syndrome is characterized by severe dyspnea, which is often associated with bronchospasm and hypoxia. This can also be related to respiratory failure and death. Patients with a history of pulmonary insufficiency or those with pulmonary tumor infiltration may be at a greater risk of poor outcomes.<br>Postmarketing studies have identified fatal bronchiolitis obliterans and ILD.                                                                                                                | Advise patients to contact their healthcare provider immediately for symptoms of infusion-related reactions, such as sudden cough and breathing problems, and infections, such as flu symptoms with cough. (Genentech, 2022c)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Monoclonal antibodies: human                     | Daratumumab (anti-CD38 antibody; Darzalex <sup>®</sup> )         | Upper respiratory infection; pneumonia, infusion-related reactions; systemic administration-related reactions, including respiratory symptoms (e.g., bronchospasm, nasal congestion, cough [may be productive], throat irritation, allergic rhinitis, and wheezing); cough; dyspnea; pulmonary edema<br>Infections include bronchiolitis, bronchitis, viral bronchitis, respiratory syncytial virus, tracheobronchitis, atypical pneumonia, bronchopulmonary aspergillosis, lung infection, <i>Pneumocystis jirovecii</i> pneumonia, aspiration pneumonia, <i>Streptococcus</i> pneumonia, viral pneumonia, and pulmonary mycosis. | Postmedication recommended for patients with a history of COPD includes consideration of short- and long-acting bronchodilators and inhaled corticosteroids following the first 4 doses of medication. Consider discontinuing these additional postmedications if patients do not experience a major systemic administration-related reaction.<br>For infusion-related reactions of any grade or severity, immediately interrupt the infusion and manage symptoms.<br>For grade 1–2 (mild to moderate) events, once reaction symptoms resolve, resume the infusion at no more than half the rate at which the reaction occurred. If patients do not experience any further reaction symptoms, infusion rate escalation may resume at increments and intervals as clinically appropriate (up to the maximum rate of 200 ml/hour). |

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**TABLE 17-1.** Pulmonary Toxicities of Antineoplastic Agents (*Continued*)

| Classification                                | Drug                                                                       | Adverse Effects, Signs, and Symptoms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-----------------------------------------------|----------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Immunotherapy Agents (<i>Cont.</i>)</b>    |                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Monoclonal antibodies: human ( <i>Cont.</i> ) | Daratumumab (anti-CD38 antibody; Darzalex*) ( <i>Cont.</i> )               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | For grade 3 (severe) events, once symptoms resolve, consider restarting the infusion at no more than half the rate at which the reaction occurred. If patients do not experience additional symptoms, resume infusion rate escalation at increments and intervals as clinically appropriate. Repeat the procedure in the event of recurrence. Permanently discontinue the drug on the third occurrence of $\geq$ grade 3 reaction.<br>For grade 4 (life-threatening) events, permanently discontinue the drug.<br>Fatal infections were caused by pneumonia. (Janssen Biotech, 2022a)                                                                                          |
|                                               | Daratumumab and hyaluronidase-fihj (Darzalex Faspro®)                      | Upper respiratory infection is the most common adverse reaction and includes nasopharyngitis, respiratory syncytial virus infection, respiratory tract infection, rhinitis, tonsillitis, upper respiratory tract infection, and viral pharyngitis.<br>Pneumonia includes lower respiratory tract infection, lung infection, <i>Pneumocystis jirovecii</i> pneumonia, bacterial pneumonia, cough (may be productive), dyspnea, bronchitis, pulmonary edema, influenza, systemic administration-related reactions (e.g., respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing), and respiratory failure. | Postmedication recommended for patients with a history of COPD includes consideration of short- and long-acting bronchodilators and inhaled corticosteroids following the first 4 doses of medication. Consider discontinuing these additional postmedications if patients do not experience a major systemic administration-related reaction. Advise patients to seek immediate medical attention for any signs and symptoms of systemic administration-related reactions, including cough, shortness of breath, or difficulty breathing. (Janssen Biotech, 2022b)                                                                                                            |
|                                               | Ofatumumab (anti-CD20 antibody; Arzerra®) for chronic lymphocytic leukemia | Upper and lower respiratory tract infections, pneumonia, cough, dyspnea, bronchitis, infusion-related reaction (e.g., bronchospasm, pulmonary edema, dyspnea)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Infusion-related reactions occur more frequently with the first 2 infusions. To prevent infusion-related reactions, premedicate with acetaminophen, an antihistamine, and a corticosteroid. Infusion-related reactions may occur despite premedication. Interrupt infusion for infusion-related reactions of any severity. Institute medical management for severe infusion-related reactions. If an anaphylactic reaction occurs, immediately and permanently discontinue the drug and initiate appropriate medical treatment. Advise patients to contact their healthcare provider for any signs of infections, including fever and cough. (Novartis Pharmaceuticals, 2021b) |

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**TABLE 17-1.** Pulmonary Toxicities of Antineoplastic Agents (*Continued*)

| Classification                                | Drug                                                           | Adverse Effects, Signs, and Symptoms                                                                                                                                                                                                                                                                       | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-----------------------------------------------|----------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Immunotherapy Agents (Cont.)</b>           |                                                                |                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Monoclonal antibodies: human ( <i>Cont.</i> ) | Panitumumab (anti-epidermal growth factor receptor; Vectibix®) | Cough, dyspnea, ILD, infusion-related reaction (e.g., bronchospasm, dyspnea), PE                                                                                                                                                                                                                           | <p>Advise patients to contact their healthcare provider for persistent or recurrent coughing, wheezing, dyspnea, or new-onset facial swelling.</p> <p>Monitor for infusion-related reactions. Reduce infusion rate by 50% in patients experiencing a mild or moderate (grade 1–2) infusion-related reaction for the duration of that infusion. Terminate the infusion in patients experiencing severe infusion-related reactions. Depending on the severity or persistence of the reaction, permanently discontinue the drug.</p> <p>If acute onset or worsening pulmonary symptoms occur, hold the drug. Discontinue therapy if ILD is confirmed.</p> <p>In patients with a history of interstitial pneumonitis or pulmonary fibrosis or evidence of interstitial pneumonitis or pulmonary fibrosis, the drug's benefits versus the risk of pulmonary complications must be carefully considered.</p> <p>When the drug is combined with chemotherapy and bevacizumab, an increased incidence of PE exists. (Amgen, 2021c)</p> |
| Monoclonal antibodies: humanized              | Alemtuzumab (anti-CD52 antibody; Campath®)                     | Dyspnea of uncertain significance, bronchospasm, interstitial pneumonitis, asthma, bronchitis, COPD, hemoptysis, hypoxia, pleural effusion, pleurisy, pulmonary edema, pulmonary fibrosis, pulmonary infiltration, respiratory depression, respiratory insufficiency, sinusitis, stridor, throat tightness | <p>Advise patients to report signs of lung disease such as shortness of breath, cough, wheezing, chest pain or tightness and hemoptysis. (Genzyme, 2021)</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                                               | Bevacizumab (Avastin®)                                         | Hemoptysis, pulmonary bleeding (serious and fatal occurred more often in patients with squamous cell lung cancer), infusion-related reactions (e.g., wheezing, oxygen desaturation), pneumonitis, pulmonary infiltrates                                                                                    | <p>If grade 3–4 hemoptysis occurs, discontinue the drug therapy.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                                               | Bevacizumab-awwb (Mvasi®; biosimilar to bevacizumab)           | The use of bevacizumab increases the risk of radiation-induced lung injury.                                                                                                                                                                                                                                | <p>If there is a recent history of hemoptysis of 1/2 teaspoon (2.5 ml) or more, withhold the drug.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                               | Bevacizumab-bvzr (Zirabev™; biosimilar to bevacizumab)         |                                                                                                                                                                                                                                                                                                            | <p>For grade 4 venous thromboembolism (including PE), discontinue the drug. Decrease the rate of infusion for mild, clinically insignificant infusion-related reactions. Interrupt the infusion in patients with clinically significant infusion-related reactions and consider resuming at a slower rate following resolution. Discontinue in patients who develop a severe infusion-related reaction and administer appropriate medical therapy. (Amgen, 2021b; Genentech, 2021b; Lind et al., 2012; Pfizer, 2021d)</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|                                               | Elotuzumab (Empliciti®)                                        | Cough, nasopharyngitis, upper respiratory tract infection, pneumonia                                                                                                                                                                                                                                       | (Bristol-Myers Squibb, 2022a)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

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**TABLE 17-1.** Pulmonary Toxicities of Antineoplastic Agents (*Continued*)

| Classification                                    | Drug                                                                                                                                         | Adverse Effects, Signs, and Symptoms                                                                                                                                                                                                                                                                                          | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|---------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Immunotherapy Agents (Cont.)</b>               |                                                                                                                                              |                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Monoclonal antibodies: humanized ( <i>Cont.</i> ) | Obinutuzumab (Gazyva <sup>®</sup> )                                                                                                          | Cough, dyspnea, infusion-related reactions, respiratory symptoms (e.g., bronchospasm, larynx and throat irritation, wheezing, laryngeal edema), hypersensitivity reaction, upper and lower respiratory infection, pneumonia                                                                                                   | See package insert for instructions regarding premedication to prevent and treat infusion-related reactions. (Genentech, 2022b)                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                   | Pertuzumab (Perjeta <sup>®</sup> )                                                                                                           | Upper respiratory infection, dyspnea, cough, infusion-related reactions                                                                                                                                                                                                                                                       | Advise patients to contact their healthcare provider immediately for new-onset or worsening shortness of breath, or cough due to concern for left ventricular dysfunction. (Genentech, 2020d)                                                                                                                                                                                                                                                                                                                                                |
|                                                   | Pertuzumab, trastuzumab, and hyaluronidase-zxxf (Phesgo <sup>™</sup> )                                                                       | Dyspnea, cough, interstitial pneumonitis, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, pulmonary insufficiency and hypoxia, ARDS, pulmonary fibrosis                                                                                                                                            | Administration can result in serious and fatal pulmonary toxicity similar to trastuzumab. Patients with symptomatic ILD or with extensive tumor involvement of the lungs, resulting in dyspnea at rest, appear to have more severe toxicity. Discontinue the drug for anaphylaxis, angioedema, interstitial pneumonitis, or ARDS. (Genentech, 2020a)                                                                                                                                                                                         |
|                                                   | Polatuzumab vedotin-piiq (Polivy <sup>™</sup> ; CD79b-directed antibody–drug conjugate)                                                      | Pneumonia, dyspnea, infusion reaction with dyspnea, bronchospasm and wheezing, upper respiratory infection, pneumonitis                                                                                                                                                                                                       | For the first instance of grade 3 wheezing, bronchospasm, or generalized urticaria, permanently discontinue the drug. Permanently discontinue the drug for recurrent grade 2 wheezing or urticaria or for recurrence of any grade 3 symptoms. Fatal or severe infections have occurred, including opportunistic infections such as sepsis, <i>Pneumocystis jirovecii</i> pneumonia, and other fungal pneumonia. Administer prophylaxis for <i>Pneumocystis jirovecii</i> pneumonia and herpes virus throughout treatment. (Genentech, 2020c) |
|                                                   | Tafasitamab-cxix (Monjuvi <sup>®</sup> ; CD19-directed cytolytic antibody)                                                                   | Cough, respiratory tract infection, infusion reaction with dyspnea, bronchitis, pneumonia, exacerbation of COPD                                                                                                                                                                                                               | Fatal and severe infections have occurred, including opportunistic infection. Monitor patients for signs and symptoms of infection and manage infections as appropriate. Based on the severity of the infusion-related reaction, interrupt or discontinue the drug. (MorphoSys, 2021)                                                                                                                                                                                                                                                        |
|                                                   | Trastuzumab (Herceptin <sup>®</sup> )<br>HER2 receptor antagonist<br><br>Trastuzumab-pkrb (Herzuma <sup>®</sup> ; biosimilar to trastuzumab) | Infusion reaction, pulmonary toxicity, dyspnea, cough, interstitial pneumonitis, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, pulmonary insufficiency and hypoxia, ARDS, pulmonary fibrosis<br><br>These symptoms can occur as a result of an infusion reaction.<br>Upper respiratory infection | Stop the infusion for dyspnea or clinically significant hypotension concerning infusion reaction. Provide medical treatment as indicated, which may include epinephrine, corticosteroids, diphenhydramine, bronchodilators, and oxygen.<br>Discontinue medication for anaphylaxis, angioedema, interstitial pneumonitis, or ARDS.                                                                                                                                                                                                            |

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**TABLE 17-1.** Pulmonary Toxicities of Antineoplastic Agents (*Continued*)

| Classification                                    | Drug                                                                                | Adverse Effects, Signs, and Symptoms                                                                                                                                                                                             | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|---------------------------------------------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Immunotherapy Agents (Cont.)</b>               |                                                                                     |                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Monoclonal antibodies: humanized ( <i>Cont.</i> ) | Trastuzumab-dttb (Ontruzant <sup>®</sup> ; biosimilar to trastuzumab)               |                                                                                                                                                                                                                                  | <p>Patients with symptomatic ILD or extensive tumor involvement of the lungs, resulting in dyspnea at rest, may be at greater risk for severe reactions. Adverse effects increase with combined drug therapy. (Amgen 2019; Genentech, 2021c; Merck, 2022b; Mylan Pharmaceuticals, 2021; Pfizer, 2022)</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|                                                   | Trastuzumab-anns (Kanjinti <sup>™</sup> ; biosimilar to trastuzumab)                |                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                   | Trastuzumab-qyyp (Trazimera <sup>™</sup> ; biosimilar to trastuzumab)               |                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                   | Trastuzumab-dkst (Ogivri <sup>®</sup> ; biosimilar to trastuzumab)                  |                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                   | Trastuzumab and hyaluronidase-oysk (Herceptin <sup>®</sup> , Hylecta <sup>™</sup> ) | Dyspnea, interstitial pneumonitis, upper respiratory tract infection, bronchitis, cough, pulmonary infiltrates, pleural effusions, noncardiogenic pulmonary edema, pulmonary insufficiency and hypoxia, ARDS, pulmonary fibrosis |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Antibody–drug conjugate                           | Fam-trastuzumab deruxtecan-nxki (Enhertu <sup>®</sup> )                             | ILD, pneumonitis, cough, dyspnea, upper respiratory tract infection, pneumonia                                                                                                                                                   | <p>Administration can result in serious and fatal pulmonary toxicity. Symptoms usually occur during or within 24 hours of administration. Patients with symptomatic ILD or with extensive tumor involvement of the lungs, resulting in dyspnea at rest, appear to have more severe toxicity. Discontinue for anaphylaxis, angioedema, interstitial pneumonitis, or ARDS. (Genentech, 2020b, 2021c)</p> <p>Advise patients to immediately report cough, dyspnea, fever, or any new or worsening respiratory symptoms. Monitor for and promptly investigate signs and symptoms, including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Evaluate patients with suspected ILD by radiographic imaging and consider a consultation with a pulmonologist. For grade 1 asymptomatic ILD or pneumonitis, interrupt the drug until resolved to grade 0. If resolved in <math>\leq 28</math> days from onset, maintain the dose. If resolved <math>&gt; 28</math> days from onset, reduce the dose by one level. Consider corticosteroid treatment as soon as ILD and pneumonitis are suspected. Permanently discontinue the drug in all patients with a <math>\geq</math> grade 2 ILD or pneumonitis. Advise patients of the risk and to report symptoms immediately. Promptly initiate systemic corticosteroid treatment and continue for at least 14 days followed by a gradual taper for at least 4 weeks. (Daiichi Sankyo, 2021)</p> |

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**TABLE 17-1.** Pulmonary Toxicities of Antineoplastic Agents (*Continued*)

| Classification                              | Drug                                           | Adverse Effects, Signs, and Symptoms                                                                                                                              | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|---------------------------------------------|------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Immunotherapy Agents (Cont.)</b>         |                                                |                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Antibody–drug conjugate<br>( <i>Cont.</i> ) | Loncas-tuximab<br>tesirine-lpyl<br>(Zynlonta™) | Pleural effusion, dyspnea                                                                                                                                         | Hold the drug for edema or effusions $\geq$ grade 2 until it resolves to $\leq$ grade 1.<br>If dosing is delayed by more than 3 weeks due to toxicity related to the drug, reduce subsequent doses by 50%. If toxicity reoccurs following dose reduction, consider discontinuation of the drug.<br>Consider diagnostic imaging in patients who develop symptoms of pleural effusion and institute appropriate management.<br>(ADC Therapeutics, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Bispecific antibody                         | Amivantamab-vmjw<br>(Rybrevant®)               | ILD, pneumonitis, dyspnea, cough, infusion-related reaction                                                                                                       | Monitor for infusion-related reactions.<br>If grade 1–2 infusion-related reaction occurs, interrupt the infusion and monitor patients until the reaction symptoms resolve.<br>Resume the infusion at 50% of the infusion rate. If there are no additional symptoms after 30 minutes, the infusion rate may be escalated. Include corticosteroids with premedications for subsequent doses.<br>If grade 3 reaction occurs, interrupt the infusion and administer supportive care medications. Monitor patients until reaction symptoms resolve. Resume the infusion at 50% of the infusion rate. If there are no additional symptoms after 30 minutes, the infusion rate may be escalated. Include corticosteroids with premedications for subsequent doses. For recurrent grade 3 reactions, permanently discontinue the drug.<br>Advise patients to contact their healthcare provider for new or worsening symptoms indicative of ILD or pneumonitis (e.g., dyspnea, cough, fever).<br>Hold medication for suspected ILD and pneumonitis.<br>For any grade ILD or pneumonitis, hold the drug. Permanently discontinue the drug if ILD or pneumonitis is confirmed.<br>(Janssen Biotech, 2022c) |
| Chimeric antigen receptor T-cell therapy    | Axicabtagene ciloleucel<br>(Yescarta®)         | Hypoxia, cough, dyspnea, pleural effusion, pulmonary edema, pneumonia, respiratory failure, cytokine release syndrome, infusion-related reaction                  | Manage cytokine release syndrome per medication prescribing information.<br>(Kite Pharma, 2022b)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                             | Brexucabtagene autoleucel<br>(Tecartus™)       | Hypoxia, cough, dyspnea, pleural effusion, respiratory failure, pulmonary edema, pneumonitis, cytokine release syndrome, infusion-related reaction                | Manage cytokine release syndrome per medication prescribing information.<br>(Kite Pharma, 2022a)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                             | Idecabtagene vicleucel<br>(Abecma®)            | Hypoxia, cough, pneumonia, dyspnea, acute respiratory failure, pulmonary edema, upper respiratory infection, cytokine release syndrome, infusion-related reaction | Manage cytokine release syndrome per medication prescribing information.<br>(Cephalon, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

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**TABLE 17-1.** Pulmonary Toxicities of Antineoplastic Agents (*Continued*)

| Classification                                             | Drug                                              | Adverse Effects, Signs, and Symptoms                                                                                                                 | Nursing Considerations                                                                                     |
|------------------------------------------------------------|---------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|
| <b>Immunotherapy Agents (Cont.)</b>                        |                                                   |                                                                                                                                                      |                                                                                                            |
| Chimeric anti-gen receptor T-cell therapy ( <i>Cont.</i> ) | Lisocabtagene maraleucel (Breyanzi <sup>®</sup> ) | Hypoxia, cough, dyspnea, pleural effusion, upper respiratory tract infection, cytokine release syndrome, infusion-related reaction                   | Manage cytokine release syndrome per medication prescribing information. (Juno Therapeutics, 2021)         |
|                                                            | Tisagenlecleucel (Kymriah <sup>®</sup> )          | Hypoxia, cough, dyspnea, pulmonary edema, pleural effusion, ARDS, lung infiltration, tachypnea, cytokine release syndrome, infusion-related reaction | Manage cytokine release syndrome per medication prescribing information. (Novartis Pharmaceuticals, 2022b) |

ARDS—acute respiratory distress syndrome; COPD—chronic obstructive pulmonary disease; ILD—interstitial lung disease; IV—intravenous; MASCC—Multinational Association of Supportive Care in Cancer; PE—pulmonary embolism; PFTs—pulmonary function tests; VOD—veno-occlusive disease

c) Risk factors for direct injury

- (1) Rare reports of interstitial pulmonary infiltrates and acute alveolitis with hydroxyurea have been noted.
- (2) Metabolic injury
  - (a) Metabolites of cyclophosphamide cause acute pneumonitis that may be hemorrhagic.
  - (b) Renal dysfunction may cause delayed drug excretion and increase the pulmonary toxicity of bleomycin, cyclophosphamide, and methotrexate (Leger et al., 2017; Stein et al., 2015).
- (3) Disruption of intracellular kinases
  - (a) Tyrosine kinase inhibitors (Ohmori et al., 2021; Teuwen et al., 2015)
  - (b) Epidermal growth factor receptor inhibitors (Tewwen et al., 2015)
  - (c) Mammalian target of rapamycin inhibitors: Genetic risks may be activated by these agents (Nishino et al., 2016; Teuwen et al., 2015; Willemsen et al., 2016).
- (4) Cytotoxic antigen-directed T-cell responses may drive lung changes with immunotherapy (Q. Zhang et al., 2021).
- (5) Pulmonary edema
  - (a) Interleukin-2 is associated with a high incidence of capillary leak syndrome. Pulmonary edema is a dose-limiting toxicity of high-dose interleukin-2 therapy. Severity depends on the route, dose, and administration schedule (Dhupkar & Gordon, 2017). It resolves quickly after therapy ends and diuresis begins.
  - (b) Docetaxel is associated with fluid retention, alveolar permeability, and

pulmonary infiltrates. These symptoms may be prevented with corticosteroid premedication and are treated with diuretics (Leger et al., 2017).

- (c) Cytosine arabinoside, intermediate and high dose, can affect pulmonary function (Nucci et al., 2015).
- (d) Leuprolide acetate has been reported to cause varying degrees of ILD (AbbVie, 2022).
- (e) Tyrosine kinase inhibitors cause capillary permeability, pulmonary edema, and effusions (Dasgupta et al., 2017; Medeiros et al., 2018; Teuwen et al., 2015).
- (6) Hypersensitivity pneumonitis
  - (a) Paclitaxel can cause acute pneumonitis, which no longer appears to be related to the drug's emulsification agents (polyoxyl 40 hydrogenated castor oil [Kolliphor<sup>®</sup> EL, formerly Cremophor<sup>®</sup> EL]) as originally postulated (Nakamura et al., 2021).
  - (b) Docetaxel has an increased risk of hypersensitivity pneumonitis with a higher total dose treatment schedule, preexisting lung disease (emphysematous or interstitial changes), and concurrent administration with gemcitabine or radiation (Genestreti et al., 2015; Grande et al., 2007).
  - (c) Gemcitabine-induced eosinophilic pneumonitis suggests that hypersensitivity may be an element of this drug reaction (De Giacomini et al., 2018).
  - (d) Acute methotrexate reaction is likely allergic (Fragoulis et al., 2019).

- (e) Pathologically confirmed hypersensitivity pneumonitis has occurred with agents such as bortezomib, imatinib, lenalidomide, mammalian target of rapamycin inhibitors, oxaliplatin, procarbazine, and thalidomide; however, no definite etiologic mechanisms have been identified (Kallel et al., 2021; Leger et al., 2017; Teuwen et al., 2015; Toma et al., 2017). This is not a comprehensive list. Please refer to Table 17-1 for specific agent information.
  - (f) Hypersensitivity skin testing can differentiate the etiology when multiple agents are implicated (Kuo et al., 2015).
- 5. Clinical manifestations: may be difficult to detect when subtle
  - a) Signs and symptoms (Brahmer et al., 2021; Johkoh et al., 2021; NCCN, 2022a; Rapoport et al., 2021)
    - (1) Dyspnea
    - (2) Dry cough
    - (3) Low-grade fever
    - (4) Low oxygen saturation and increased oxygen requirements
    - (5) Weight loss
    - (6) Fatigue
    - (7) Crackles, wheezing, or abnormal breath sounds
    - (8) Chest pain
  - b) Timing of signs and symptoms
    - (1) Respiratory signs and symptoms vary depending on the causative agent and type of ILD.
    - (2) Onset of ILD is sooner with chemotherapy than with targeted therapies (e.g., kinase inhibitors) and immune checkpoint inhibitors (Iwashita et al., 2021).
    - (3) Acute hypersensitivity pneumonitis reactions with chemotherapy agents, such as gemcitabine and methotrexate, may occur as early as hours to weeks after initial exposure (Samad et al., 2016; Thalambedu & El-Habr, 2020).
    - (4) Bleomycin-induced pulmonary toxicity presentation is usually subacute, with a median onset of approximately four months (O'Sullivan et al., 2003).
    - (5) Delayed toxicity may occur more than one year from drug initiation with some targeted therapies and immune checkpoint inhibitors (Skeoch et al., 2018).
- 6. Assessment
  - a) Past medical history
    - (1) Chemotherapy, targeted therapy, and immunotherapy drug exposure
    - (2) Other medications known to be associated with pulmonary toxicity (e.g., amiodarone, nitrofurantoin, disease-modifying antirheumatic drugs) (Skeoch et al., 2018)
    - (3) Radiation exposure
    - (4) Recent or chronic pulmonary conditions such as chronic obstructive pulmonary disease, preexisting ILD illness, or idiopathic pulmonary fibrosis (Skeoch et al., 2018)
    - (5) History of tobacco use (Skeoch et al., 2018)
    - (6) Advanced or metastatic cancers (Skeoch et al., 2018)
    - (7) Recent viral illnesses (e.g., COVID-19) (Cherri et al., 2021)
    - (8) Autoimmune diseases (Dodia et al., 2021)
    - (9) Occupational and environmental exposures (e.g., molds, gases, silica, asbestos, metal dust, coal) (Dodia et al., 2021; Glazer & Newman, 2004)
  - b) Physical examination (Conte et al., 2022; Johkoh et al., 2021; Leger et al., 2017)
    - (1) Tachypnea
    - (2) Crackles or wheezes on auscultation
    - (3) Cough or hemoptysis
    - (4) Accessory muscle use for breathing
    - (5) Evidence of poor tissue oxygenation in advanced cases (e.g., cyanosis, oliguria, decreased bowel sounds, altered mentation)
    - (6) Abnormal oxygen saturation readings
    - (7) Normal examination in asymptomatic patients
  - c) Performance status: Poor performance status correlates with increased risk of ILD and mortality in severe ILD (Kaku et al., 2022; Skeoch et al., 2018).
  - d) Diagnostic tests
    - (1) Diagnostic studies may show nonspecific findings, and ILD is often a diagnosis of exclusion.
    - (2) Diagnosis may be based on clinical, radiographic, and pathologic findings (Johkoh et al., 2021).
    - (3) A chest CT scan is the gold standard imaging study for drug-induced ILD (Rapoport et al., 2021).
      - (a) Chest CT scan patterns may vary based on the specific class of agents, and more than one pattern may be present (Johkoh et al., 2021).
      - (b) A CT scan may show organizing pneumonia, diffuse alveolar damage,

hypersensitivity pneumonitis, simple pulmonary eosinophilia, or nonspecific interstitial pneumonitis (Johkoh et al., 2021).

- (c) The most common pattern is hypersensitivity pneumonitis, followed by organizing pneumonia, and then diffuse alveolar damage (Kaku et al., 2022).
- (4) Pulmonary function test (PFT) for diagnosis of ILD may be useful but lacks specificity, and accuracy is variable (Skeoch et al., 2018).
  - (a) Baseline PFTs are recommended for patients with Hodgkin lymphoma prior to starting bleomycin-based therapy and can be considered after four cycles of doxorubicin, bleomycin, vinblastine, dacarbazine (NCCN, 2022b).
  - (b) If PFTs are performed, they should include spirometry and diffusing capacity of the lungs for carbon dioxide (DLCO) (Brahmer et al., 2021).
  - (c) Reductions in DLCO are the primary change noted in PFTs following bleomycin (Roncolato et al., 2016).
  - (d) PFTs are typically normal in immune checkpoint inhibitor pneumonitis (Rapoport et al., 2021).
- (5) Numerous biomarkers, including Krebs von den Lungen-6 (KL-6) and surfactant protein D (SP-D), and tissue-based genetic signatures have shown promise as a diagnostic tool for general ILD; however, no specific diagnostic biomarker exists for drug-induced ILD (Bowman et al., 2021; Okamoto et al., 2015).
  - (a) KL-6 has also been shown to be a predictive biomarker for ILD severity and poor outcomes (T. Zhang et al., 2021b).
  - (b) KL-6 to Sialyl-Lewis X antigen (SLX) (K/S) ratio may predict lung underlying idiopathic interstitial pneumonia in patients with cancer who are at higher risk for the development of drug-induced ILD (Kashiwabara et al., 2015).
  - (c) Whole-genome sequencing has been studied as a tool for pinpointing predictive biomarkers in drug-induced ILD (Udagawa et al., 2019).
- (6) A positron-emission tomography–CT scan has been evaluated in case series

of drug-induced interstitial pneumonitis from chemotherapy, immunotherapy, and targeted therapies (Dejust et al., 2018; Lu & Yang, 2021). The role of this diagnostic tool is still unclear, as findings from pneumonitis can mimic hypermetabolic findings present in infection and malignancy (Kalisz et al., 2019).

- (7) Bronchoscopy with lavage findings are usually nonspecific and primarily used to rule out other causes (e.g., infection, underlying malignancy) (NCCN, 2022a; Skeoch et al., 2018).
- (8) Open lung biopsy may also be useful in specific cases when other causes need to be ruled out; however, little evidence exists to support its use in most cases (Skeoch et al., 2018).
- 7. Collaborative management
  - a) PFTs should be considered for the following patients being evaluated for therapy.
    - (1) Patients with baseline lung disease (e.g., chronic obstructive pulmonary disease, ILD) and those with prior treatment-induced pulmonary toxicities (NCCN, 2022a)
    - (2) Prior to bleomycin-based chemotherapy for Hodgkin lymphoma (NCCN, 2022b)
  - b) Avoid exceeding maximum recommended doses.
    - (1) Bleomycin: 400 units total lifetime dose (Hospira, 2021a)
    - (2) Mitomycin C: 20 mg/m<sup>2</sup> (Accord Healthcare, 2018)
  - c) Consider alternative regimens and dosing schedules for high-risk patients.
    - (1) Bleomycin should be avoided in patients with testicular cancer older than age 50 years, who have underlying lung disease, or are at risk for pulmonary complications (NCCN, 2022c). Proceed with caution in patients with a prior heavy smoking history and underlying kidney disease.
    - (2) Bleomycin should be used with caution in patients with Hodgkin lymphoma aged 60 years and older. Alternative regimens without bleomycin should be considered (NCCN, 2022b).
    - (3) Eliminating bleomycin in a doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) regimen after two cycles in Hodgkin lymphoma has resulted in reduced pulmonary toxicity without reduced efficacy (Johnson et al., 2016).
  - d) If pulmonary toxicity is suspected, hold the agent and notify the prescriber. Rechallenge with the

offending agent varies with toxicity severity, timing, probable mechanism of injury, and specific agent.

e) Consider PFTs for patients with new pulmonary symptoms suggestive of ILD or in asymptomatic individuals with radiographic findings of pneumonitis (Conte et al., 2022; Rapoport et al., 2021).

f) Administer oxygen for hypoxic patients (Conte et al., 2022).

(1) Patients who have received bleomycin should avoid high oxygen concentrations, including general anesthesia (Watson et al., 2018).

(2) Bleomycin produces free oxygen radicals, and high oxygen concentrations may cause respiratory complications. Case reports of respiratory failure in patients who received prior bleomycin have been reported (Brasher & Sood, 2020).

g) Mechanical ventilation may be required in severe cases, considering the patient's overall prognosis (Conte et al., 2022).

h) Establish fluid balance goals.

(1) Carefully record intake and output.

(2) Determine if fluid boluses or fluid restrictions are warranted.

(3) Consider using goal dry weight to target diuretic therapy. Weigh patients regularly.

i) Supportive care

(1) Oxygen therapy

(a) Establish a target level based on the degree of hypoxemia (Conte et al., 2022).

(b) Avoid high oxygen concentrations in patients who have received bleomycin (Watson et al., 2018).

(2) Dyspnea management (Shelton et al., 2019)

(a) Immediate-release opioids

(b) Fans

(c) Noninvasive ventilation

(d) Psychoeducational interventions

(e) Oral nutritional interventions

j) Treatment of ILD

(1) Administer corticosteroids as ordered. Corticosteroids usually are contraindicated for patients receiving lymphokines, such as aldesleukin (Dhupkar & Gordon, 2017).

(a) Corticosteroids are administered in low, moderate, or high doses.

(b) The risks and benefits of corticosteroids should be considered when treating pulmonary toxicities.

(c) Exact dosages remain controversial, but specific recommendations based

on toxicity grade have been established for immune checkpoint inhibitors (NCCN, 2022a).

(d) Consider adding infliximab, IV immunoglobulin, or mycophenolate mofetil for immune checkpoint inhibitor-induced ILD if there is no response to corticosteroids after 48 hours (NCCN, 2022a).

(2) Initiate antimicrobial therapy when infection superimposed on other lung toxicity is suspected (NCCN, 2022a).

k) Follow-up evaluation

(1) Frequency is based on the severity of and risk for ILD and may increase with cumulative dose or added risk factors.

(2) Patients should be followed for symptoms for at least two months after chemotherapy (Iwashita et al., 2021).

(3) Patients receiving targeted therapies and immune checkpoint inhibitors need to be followed longer given the later onset of pulmonary toxicities that can be seen with these agents (Iwashita et al., 2021).

(4) A post-treatment chest CT scan is recommended for patients receiving more than 300 units of bleomycin (Watson et al., 2018).

(5) Certain patients at risk for ILD should be periodically monitored with specific PFTs.

(a) Routine PFT screening may be useful in allogeneic hematopoietic stem cell transplantation (HSCT) recipients. The testing frequency has not been clearly determined, but some experts have recommended every three months for the first two years (Jamani et al., 2020; Thompson et al., 2014).

(b) A symptom-based follow-up approach is preferred over routine monitoring with PFTs in patients who have received bleomycin (Roncolato et al., 2016; Watson et al., 2018).

(c) PFTs should include spirometry and DLCO (Brahmer et al., 2021).

(d) Drug-induced ILD shows a restrictive spirometry picture with reductions in total lung capacity similar to other forms of ILD. DLCO is also reduced in drug-induced ILD, although the sensitivity for this measure may be low (Bui et al., 2020; Conte et al., 2022).

- (6) In patients with acute-onset symptomatic disorders, such as alveolar hemorrhage or acute hypersensitivity reaction, screening is not performed because of the usual acute presentation.
- (7) Late or delayed onset of lung toxicity may occur and be related to treatment and host factors, but plans for follow-up care are not clearly defined (Versluys & Bresters, 2016).

### C. Diffuse alveolar hemorrhage

#### 1. Pathophysiology

- a) Diffuse alveolar hemorrhage is a rare and life-threatening disease characterized by bleeding in the microvasculature of small airways. It is separated into four major groups.

- (1) Immune associated
- (2) Congestive heart failure associated
- (3) Miscellaneous (i.e., infection, trauma, clotting disorder, drugs, malignancy, and HSCT)
- (4) Idiopathic

- b) The major pathologic findings of diffuse alveolar hemorrhage include the following (J.A. Park, 2021).

- (1) Bland pulmonary hemorrhage is associated with the leaking of red blood cells into the alveoli without damage or inflammation. It commonly occurs with coagulopathies, anticoagulant therapy, heart failure, or renal failure.
- (2) Diffuse alveolar damage occurs due to direct lung injury that causes alveolar edema and the development of hyaline membranes and can lead to alveolar hemorrhage. Numerous causes include cytotoxic and noncytotoxic drugs, infections (e.g., COVID-19), and radiation treatment (e.g., thoracic or total body irradiation).
- (3) Antibody-mediated pulmonary capillaritis is characterized by neutrophilic infiltration of the interstitium of the lung and fibrinoid necrosis.

#### 2. Incidence

- a) Alveolar hemorrhage incidence rates have been reported as infrequent, occurring in 1.1% of autologous HSCT recipients and 7.2% in allogeneic HSCT recipients (Z. Zhang et al., 2021).
- b) Incidence is rare with other antineoplastic therapies.

#### 3. Risk factors

- a) Alveolar hemorrhage in patients with cancer is most commonly documented in HSCT. It is associated with allogeneic HSCT, myeloablative con-

ditioning, severe graft-versus-host disease, and older age. Mortality in HSCT recipients is more than 80% (Z. Zhang, 2021c).

- b) Alveolar hemorrhage has been rarely associated with standard doses of bevacizumab, bortezomib, crizotinib, cyclophosphamide, docetaxel, etoposide, everolimus, gefitinib, gemcitabine, lenalidomide, nilotinib, oxaliplatin, pemetrexed, rituximab, and sirolimus (Chatterjee et al., 2015; Donatelli et al., 2014; Kurimoto et al., 2015; Maldonado et al., 2022c; Mankikian et al., 2014; Ono et al., 2013; Sakai et al., 2015; Saleem et al., 2015; Specks, 2022; Sugita et al., 2015; Toma et al., 2017; Wirk, 2012; Willemsen et al., 2016).

- c) Concomitant pulmonary infection may be present with adenovirus, COVID-19, cytomegalovirus, dengue fever, Epstein-Barr virus, *Stenotrophomonas maltophilia*, and *Strongyloides* (parasite) (Loecher et al., 2021; J.A. Park, 2021).

- d) Non-oncologic drugs can cause alveolar hemorrhage (e.g., amiodarone, crack cocaine, nitrofurantoin, propylthiouracil, valproate) (J.A. Park, 2021).

- e) Unlike other bleeding syndromes, pulmonary hemorrhage is not always related to platelet counts or coagulation values (Nanjappa et al., 2016).

#### 4. Clinical manifestations (Loecher et al., 2021)

- a) Symptoms include dyspnea, fever, cough, chest discomfort, and profound hypoxemia.
- b) Hemoptysis occurs in up to one-third of patients. Pink, frothy sputum and blood in bronchoalveolar specimens may be found.
- c) Hypoxemia-related symptoms include agitation, confusion, air hunger, cyanosis, tachycardia, and bradycardia.

#### 5. Assessment

- a) Early crackles and diminished breath sounds as the airways become filled with bloody exudate
- b) Decreased oxygen saturation
- c) Increase in quantity and change in the quality of sputum
- d) Hemoglobin, platelet count, and coagulation parameters: Hemoglobin may not fall until bleeding is life threatening.
- e) Nonspecific findings of inflammation, including increased erythrocyte sedimentation rate and leukocytosis (if not marrow suppressed)
- f) PFTs (increased DLCO with hypoxemia) if patients can participate (Loecher et al., 2021)
- g) Chest x-ray or CT scan to evaluate for diffuse interstitial and alveolar infiltrates (typically nonspecific) (Loecher et al., 2021)
- h) Bronchoalveolar lavage (bloody returns that increase during lavage)



## 6. Collaborative management

- a) Corticosteroids are the standard treatment for diffuse alveolar hemorrhage, as it is thought to be inflammatory (Loecher et al., 2021). Methylprednisolone at doses of 30 mg/kg daily or 500–2,000 mg daily via IV for approximately three to five days followed by a taper is the typical treatment (J.A. Park, 2021). Further study is needed to determine the optimal dose of corticosteroids.
- b) Coagulation factors can be administered adjunctively, although no one therapy has proved effectively. Unproven coagulation therapies are IV aminocaproic acid and recombinant factor VIIa (Loecher et al., 2021).
- c) Etanercept is a tumor necrosis factor-alpha inhibitor that blocks pulmonary fibrosis formation and has been studied in patients with diffuse alveolar hemorrhage after HSCT with corticosteroids (Loecher et al., 2021).
- d) Consider noninvasive or invasive mechanical ventilation with positive pressure to produce intra-alveolar pressure and reduce bleeding (J.A. Park, 2021).
- e) Provide supportive management of dyspnea.

## D. Acute promyelocytic leukemia (APL) treatment-related differentiation syndrome (DS)

## 1. Pathophysiology

- a) APL treatment-related DS occurs with APL, a type of leukemia in which leukemic cells are halted at the promyelocyte stage. This DS was initially named retinoic acid syndrome because of its association with the administration of all-trans retinoic acid. This modified term was introduced because the syndrome occurs with any differentiating agents, such as arsenic trioxide (Stahl & Tallman, 2019). This syndrome has also been reported in patients with acute myeloid leukemia undergoing treatment with newer targeted agents, such as fms-related receptor tyrosine kinase 3 (FLT3) and isocitrate dehydrogenase (IDH) inhibitors (Fathi et al., 2021).
- b) The pathogenesis of APL treatment-related DS is complex and not completely understood. Interleukin-1, -6, and -8 and tumor necrosis factor-alpha lead to systemic inflammatory response syndrome. The release of cathepsin G leads to increased vascular permeability, which causes endothelial damage, and the increased adhesion of blast cells leads to leukostasis, endothelial damage, and organ infiltration (Stahl & Tallman, 2019).
- c) It is more a condition of tumor responsiveness to therapy than a toxicity.

## 2. Incidence

- a) APL treatment-related DS occurs in approximately 27%–48% of patients with APL receiving induction therapy (Elemam & Abdelmoety, 2013; Larson & Bag, 2022; Leblejian et al., 2013; Lengfelder et al., 2015).
- b) It is more prevalent in patients with high white blood cell counts (Watts & Tallman, 2014).
- c) The overall incidence of DS in patients with acute myeloid leukemia (non-APL) being treated with an IDH inhibitor is approximately 19% and is associated with a latent onset compared with APL (Fathi et al., 2021).
  - (1) Gilteritinib, an FLT3 inhibitor, includes a black box warning for DS. It promotes cellular differentiation to a more mature myeloid lineage. The time to onset is 2–75 days (Fathi et al., 2021).
  - (2) Ivosidenib, an IDH1 inhibitor, includes a black box warning for DS. The median time to onset is 29 days (range of 5–59 days). Enasidenib, another IDH1 inhibitor, is associated with a 14% incidence of DS (Fathi et al., 2021). DS has been observed as early as one day and up to five months after initiation of enasidenib (Celgene, 2020b).

## 3. Risk factors

- a) Increased body mass index is the only validated risk factor for DS (Breccia et al., 2012; Leblejian et al., 2013).
- b) High white blood cell count may be associated with increased risk. A rapid rise in white blood cell count, or a large percentage of immature cells, is related to the presence of APL treatment-related DS (Larson & Bag, 2022; Leblejian et al., 2013; Watts & Tallman, 2014).
- c) Acute myeloid leukemia, M3 subtype, expression of CD13 on APL blast cells (Breccia et al., 2014)
  - (1) The CD34/CD2 subgroup shows increased risk.
  - (2) CD56 expression with prevalent bcr3 expression shows increased risk.
- d) Treatment-specific variables include the following.
  - (1) All-trans retinoic acid treatment
  - (2) Arsenic trioxide
  - (3) Bortezomib
  - (4) Azacitidine (Laufer & Roberts, 2015)
  - (5) New targeted therapies (e.g., IDH1/2 inhibitors, FLT3 inhibitors)

## 4. Clinical manifestations (Stahl &amp; Tallman, 2019)

- a) Signs and symptoms include fever, dyspnea, cough, hypotension, crackles, hypoxemia, mus-



- culoskeletal pain (e.g., arthralgias, myalgias), effusions, edema, and a weight gain of more than 5 kg from baseline.
  - b) Rash can be diffuse, erythematous, and nonpruritic and is more common in severe cases (Larson & Bag, 2022).
  - c) Renal dysfunction may occur but often is slower in onset than other symptoms. It may be noted after recognizing the syndrome.
  - d) Approximately one-half of patients have symptoms within one week, and the rest develop symptoms between the third and fourth week of induction therapy (Sanz & Montesinos, 2014).
  - e) *Common Terminology Criteria for Adverse Events* grading (National Cancer Institute Cancer Therapy Evaluation Program, 2017)
    - (1) Weight gain
      - (a) Grade 1: 5% to less than 10% weight gain from baseline
      - (b) Grade 2: 10% to less than 20% weight gain from baseline
      - (c) Grade 3: greater than or equal to 20% weight gain from baseline
    - (2) The toxicity of DS is graded according to the severity of symptoms.
      - (a) Grade 1: fluid retention of less than 3 kg requiring intervention with fluid restriction or diuretics
      - (b) Grade 2: moderate signs and symptoms requiring steroid administration
      - (c) Grade 3: severe symptoms and hospitalization indicated
      - (d) Grade 4: life-threatening consequences with mechanical ventilation indicated
      - (e) Grade 5: death due to the disorder
5. Assessment
- a) Breath sounds and oxygen saturation
  - b) Intake and output (weight): monitoring of overhydration, may worsen respiratory symptoms
  - c) Laboratory studies
    - (1) White blood cell count with differential daily: Blast percentage should be assessed.
    - (2) Periodic assessment of hemoglobin, hematocrit, and platelet count: Anemia and thrombocytopenia are common.
    - (3) Periodic evaluation of coagulation parameters and platelet count: Disseminated intravascular coagulation can occur.
    - (4) Renal function tests to monitor for impairment: It is unclear if dysfunction is related to hypotension or thrombosis (Larson & Bag, 2022).
  - d) Chest x-ray or CT: nodular or ground-glass opacities with patchy bilateral distribution, consolidation, air bronchograms, prominent septal lines, and possible pleural or pericardial effusions (Stahl & Tallman, 2019)
6. Collaborative management
- a) Prevention
    - (1) Immediate administration of chemotherapy when white blood cell count rises
    - (2) Fluid management (strict intake and output)
  - b) Although no randomized studies compare patient treatment with or without steroids, retrospective studies have demonstrated that immediate use reduces DS-related mortality (Stahl & Tallman, 2019).
    - (1) If treatment with steroids is selected, the usual treatment is dexamethasone 10 mg IV twice daily. If no improvement is seen, the dexamethasone can be increased to 10 mg every six hours. Steroids can be discontinued or tapered once DS resolves.
    - (2) APL treatment-related DS presents concomitantly with infection, and a complete workup should be performed. Other diagnoses that need to be ruled out are pneumonia, heart failure, pulmonary embolism, and diffuse alveolar hemorrhage (Stahl & Tallman, 2019).
  - c) Noninvasive or invasive mechanical ventilation with positive pressure
  - d) Removal of pleural or pericardial effusions, if present
- E. Pleural effusions
1. Definition: Pleural effusions are the accumulation of excess fluid in the pleural space that impairs lung expansion. Four to six liters of pleural fluid usually pass through the potential space between the visceral and parietal pleura daily (Villena Garrido et al., 2014).
  2. Pathophysiology: Excess fluid is retained in the pleural space, restricting full alveolar expansion (Muzumdar, 2012; Villena Garrido et al., 2014).
    - a) Major causes of pleural effusion are an obstruction to fluid outflow and pleural irritation, leading to exudative capillary permeability into the space (Muzumdar, 2012).
      - (1) Mast cell degranulation may mediate pleural effusion and potential physiology for drug-related effusions (Giannou et al., 2015).
      - (2) Pleural effusions after HSCT may be multifactorial. Engraftment syndrome resulting from the treatment and cell engraft-

- ment has been associated with pleural effusions (Brownback et al., 2014).
- b) Transudative effusions are produced by passive capillary permeability and are characteristic of fluid overload, heart failure, or hypothyroidism (Dasanu et al., 2017; Kust et al., 2016).
  - c) Hydrophilic drugs with low plasma protein binding (e.g., methotrexate, pemetrexed) may accumulate in the pleural space, enhancing the incidence of pleural effusion and potentiating drug toxicity (Honoré et al., 2014).
3. Incidence of drug-related pleural effusions
    - a) Incidence varies and depends on the agent, dose, schedule, and comorbid conditions.
    - b) Incidence can be as high as 54% with some agents (Maldonado et al., 2022a, 2022b, 2022c).
  4. Risk factors
    - a) Pleural effusions are a common complication of cancer and other medical disorders, such as cirrhosis, gout, heart failure, infections, pneumonia, pulmonary embolism, renal failure, rheumatoid conditions, or hypothyroidism, and medications, such as valproate and clozapine (Jany & Welte, 2019).
    - b) When associated with chemotherapy and immunotherapy agents, pleural effusions result from capillary permeability temporally related to the administration of the offending agent. Most resolve with discontinuation of treatment.
    - c) Select chemotherapy and immunotherapy agents associated with the development of pleural effusions include the following.
      - (1) Antimetabolites and folate inhibitors (e.g., methotrexate, pemetrexed): eosinophilic pleural effusions (Cudzilo et al., 2014; Honoré et al., 2014)
      - (2) Bacillus Calmette Guérin: lymphocyte infiltration of the pleura (Tobieme et al., 2014)
      - (3) Bortezomib (Oudart et al., 2012)
      - (4) Cytosine arabinoside when combined with daunorubicin (He et al., 2014)
      - (5) Cyclophosphamide (high dose) (Nakazawa et al., 2014)
      - (6) BCR-ABL1 kinase inhibitors (e.g., dasatinib, which is the most common and significant in this drug class; imatinib; nilotinib); more common in second-generation agents (Chakraborty et al., 2013; Cortes et al., 2015; Eskazan et al., 2014; Schiffer et al., 2016)
      - (7) Docetaxel (S.I. Park et al., 2014)
      - (8) Fludarabine (Nakazawa et al., 2014)
      - (9) Gemcitabine (Kido et al., 2012)
      - (10) Immune checkpoint inhibitors (e.g., ipilimumab): late onset and uncommon; may be linked to drug-related hypothyroidism (Dasanu et al., 2017)
      - (11) Mammalian target of rapamycin inhibitors (e.g., everolimus, temsirolimus) (Fukushima et al., 2013; Willemsen et al., 2016)
      - (12) Sunitinib (Miura et al., 2014)
  5. Clinical manifestations and assessment
    - a) Patients present with tachypnea, dyspnea, increased work of breathing, abnormal chest excursion, pleuritic pain, and fatigue.
    - b) Onset varies by agent and mechanism of toxicity; hypersensitivity reactions may occur sooner than direct injury (Willemsen et al., 2016).
    - c) An upright chest x-ray documents large pleural effusions; smaller effusions are seen on a chest CT scan.
    - d) Tyrosine kinase inhibitor-induced pleural effusions are characterized by exudative features and lymphocytic infiltration of the pleura.
  6. Collaborative management (Jany & Welte, 2019)
    - a) In most cases, pleural effusions are uncomplicated and spontaneously resolve upon discontinuation of the causative agent.
    - b) Dose reduction has successfully eliminated pleural effusion related to some drugs.
    - c) Concomitant corticosteroids have effectively reduced the severity of pleural effusions related to docetaxel.
    - d) Other treatment strategies are albumin supplementation, fluid restrictions, diuretics, and corticosteroids, but these interventions do not have the evidence to support their use (Villena Garrido et al., 2014).
    - e) Medical or surgical pleurodesis is rarely required to treat drug-induced pleural effusion.
      - (1) On rare occasions, thoracentesis has been performed as a temporary measure or to rule out other causes of the effusion.
      - (2) Tunneled or temporary pleural catheters may be used with persistent pleural effusions.
- F. Patient and family education (Camp-Sorrell, 2018)
    1. Provide education regarding symptoms associated with pulmonary toxicity (e.g., cough, dyspnea, chest pain, shallow breathing, chest wall discomfort). Ensure all patients know to seek medical assistance immediately if symptoms occur.
    2. Advise smoking cessation or reduction, as any reduced exposure may reverse lung changes and slow the progression of ILD.
    3. Inform patients that treatment may be delayed or held until pulmonary symptoms resolve.

4. Explore patients' wishes regarding intubation and resuscitation status; establish advance directives.
5. Teach patients that raising the head of the bed may facilitate breathing.
6. Instruct patients to conserve energy by performing daily activities when their energy level is highest.
7. Teach patients and significant others methods to decrease symptoms of dyspnea (e.g., exercising to tolerance, practicing pursed-lip breathing, refraining from smoking, using a small fan).
8. Teach patients to take an opioid (e.g., morphine) as prescribed by their physician to relieve discomfort caused by air hunger.
9. Review the safety issues (e.g., flammability) related to oxygen administration.

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## CHAPTER 18

# Hepatic Toxicities

### A. Overview

1. More than 1,300 drugs and toxins, including anti-neoplastics and herbs, may cause liver dysfunction (Mehta, 2019; Meuneir & Larrey, 2019; Postnikov et al., 2019).
2. Functions of the liver (Bunchorntavakul & Reddy, 2017; Kalra et al., 2021; Lee & Chan, 2016; Singh et al., 2021)
  - a) Filters toxic substances
  - b) Works with the spleen to eliminate damaged red blood cells
  - c) Produces bile, which aids in absorption and digestion of fats, allowing for excretion of waste products
  - d) Synthesizes procoagulant proteins, also referred to as clotting factors (e.g., II, V, VII, IX, X, XI), which promote the maintenance of healthy homeostasis (Kujovich, 2015)
  - e) Processes and stores vitamins, minerals, proteins, fats, and glucose

### B. Pathophysiology

1. Drug toxicity mechanisms (Andrade et al., 2019; Garcia-Cortes et al., 2020; Hoofnagle & Björnsson, 2019; Lisi, 2016; Maqbool et al., 2019; Mehta, 2019; Shehu et al., 2017; Stephens & Andrade, 2020)
  - a) Intrinsic: directly affect liver; liver toxicity induced by the drug that is predictable and dose related
  - b) Idiosyncratic: occur less frequently; associated with less consistent dose-toxicity relationship and varied presentation
2. Mechanisms of injury resulting from cancer therapies (Chen et al., 2015; Mehta, 2019; Mudd & Gudati, 2021)
  - a) Disruption of hepatocytes
    - (1) Adenosine triphosphate levels decrease because of the covalent binding of drugs to intracellular proteins, leading to actin disruption.
    - (2) Disassembling actin fibrils on hepatocyte surfaces causes blebs and membrane rup-

ture, resulting in hepatic injury, inflammation, fibrosis, and carcinogenesis (Mehta, 2019).

- b) Disruption of transport proteins
    - (1) Bile flow may be interrupted by drugs affecting transport proteins at the canalicular membrane.
    - (2) Loss of villous processes and transport pump interruption prevent bile excretion, causing cholestasis.
  - c) Cytolytic T-cell activation: Immune response is stimulated by the covalent binding of drugs with cytochrome P450 (CYP) enzymes acting as an immunogen, activating T cells and cytokines and resulting in an immune response to infection or tissue damage (Frick et al., 2017; Mehta, 2019).
  - d) Apoptosis of hepatocytes: Apoptotic pathways activated by the tumor necrosis factor- $\alpha$  receptor Fas may trigger a cascade of intercellular caspases, resulting in programmed cell death.
  - e) Disruption of mitochondria: Specific drugs inhibit the synthesis of nicotinamide adenine dinucleotide and flavin adenine dinucleotide, resulting in decreased adenosine triphosphate production and interference with lipid metabolism (Neuman, 2020).
  - f) Injury of bile ducts: Toxic metabolites excreted in bile can cause injury to the bile duct epithelium (Neuman, 2020).
  - g) Hypersensitivity and immune-mediated reactions: Antigen recognition by helper T cells occurs with key cytokines (Neuman, 2020).
  - h) Genetic differences in CYP protein: These differences can result in abnormal metabolic reactions to drugs; for example, increased toxicity can occur in genetically predisposed individuals such as females or obese individuals (Mehta, 2019; Stephens & Andrade, 2020).
3. Age-specific considerations
    - a) Pediatric considerations (Ali et al., 2014; Barrett et al., 2013; Benn, 2014; Postnikov et al., 2019)

- (1) Developmental changes in liver metabolism from birth to adolescence contribute to the increased sensitivity to toxins in the pediatric population, as drug half-life is more than two to three times longer (Benn, 2014).
- (2) Plasma protein binding and partitioning are different in the pediatric population and constantly fluctuate during early years, affecting how the drug is distributed (Ali et al., 2014; Postnikov et al., 2019).
- (3) Age-related differences in pharmacokinetics, particularly in infants and neonates, are important to recognize because pH and motility affect gastrointestinal absorption, body composition alters distribution, and clearance systems are not mature (Ali et al., 2014; Benn, 2014).
- (4) Drugs known to cause hepatotoxicity in children (Barrett et al., 2013; Chalasani et al., 2021; Chen et al., 2015)
  - (a) Analgesics
  - (b) Antimicrobials
  - (c) Anticonvulsants
  - (d) Antineoplastic drugs
- (5) Frequent monitoring of liver enzymes (Barrett et al., 2013; Urrutia-Maldonado et al., 2019)

*b) Considerations for older adult patients*

- (1) Developmental changes in liver metabolism, including a decline in physiologic functions in older adults (Lucena et al., 2020; Mehta, 2019)
  - (a) Increased risk of hepatic injury
  - (b) Decreased clearance
  - (c) Drug–drug interactions
  - (d) Reduced hepatic blood flow
  - (e) Varied drug binding
  - (f) Lower hepatic volume
  - (g) Age-related changes in body composition (decrease in lean body mass and higher adipose tissue) (Lucena et al., 2020)
  - (h) Decreased bile flow and bile acid secretion (Lucena et al., 2020)
- (2) Drugs known to cause hepatotoxicity in older adults (Lucena et al., 2020; Miller et al., 2020)
  - (a) Analgesics (e.g., nonsteroidal anti-inflammatory drugs)
  - (b) Non-narcotic pain medications (e.g., tricyclic antidepressants, muscle relaxants, benzodiazepines)
  - (c) Antibiotics
  - (d) Cardiovascular drugs

- (e) Herbal therapies and dietary supplements (Miller et al., 2020)
- (f) Psychoneurotic drugs
- (g) Antituberculosis drugs
- (h) Antineoplastic drugs

**C. Incidence (see Table 18-1)**

**D. Risk factors**

1. Race: variable toxicities (Chalasani et al., 2021; Mehta, 2019)
2. Age: rare in children; increased in older adults (Chalasani et al., 2021; Chen et al., 2015; Dass, 2020; Singh et al., 2021)
3. Sex: common in females (Mehta, 2019)
4. History of alcohol use (depletes glutathione), smoking, illicit drug use (Dass, 2020; Singh et al., 2021; Vicenzi et al., 2018)
5. History of liver disease (e.g., cirrhosis, Budd-Chiari syndrome, alpha-1 antitrypsin deficiency, hemochromatosis, Wilson disease) (Hoofnagle & Björnsson, 2019; Mehta, 2019)
6. History of infections (e.g., HIV, hepatitis B, hepatitis C) (Chalasani et al., 2021; Dass, 2020; Hoofnagle & Björnsson, 2019)
7. Genetic factors: The rate of metabolism of CYP enzymes differs among individuals (Chalasani et al., 2021; Chen et al., 2015; Hoofnagle & Björnsson, 2019; Mehta, 2019).
8. Comorbidities (e.g., obesity, malnutrition, diabetes mellitus) (Mehta, 2019)
9. Drug formulations (e.g., intrahepatic chemotherapy), drug interactions, polypharmacy (e.g., noncytotoxic hepatotoxic drugs or herbal products) (Chalasani et al., 2021; Chen et al., 2015; Hoofnagle & Björnsson, 2019; Mehta, 2019)
10. History of transplantation: liver, kidney, stem cell (Mehta, 2019)
11. Prior radiation therapy (Chen et al., 2015; Mehta, 2019)

**E. Clinical manifestations**

1. Variable from asymptomatic laboratory abnormalities to acute illness to overt hepatic failure (Mehta, 2019; Shehu et al., 2017; Vicenzi et al., 2018)
2. Elevations in aminotransferases (e.g., aspartate aminotransferase, alanine aminotransferase) indicative of hepatocellular injury; portal hypertension (Mehta, 2019; Shehu et al., 2017)
3. Elevations in bilirubin, alkaline phosphatase, and gamma-glutamyl transpeptidase activity suggestive of cholestasis (Neuman, 2020; Vicenzi et al., 2018)
4. Signs and symptoms of cancer treatment–related hepatotoxicity (Andrade et al., 2019; Mehta, 2019; Shehu et al., 2017; Vicenzi et al., 2016)

**TABLE 18-1.** Hepatotoxicity of Antineoplastic Agents

| Classification             | Drug                                     | Side Effects                                                                                                                                                                                                                                                                                                                | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                |
|----------------------------|------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Chemotherapy Agents</b> |                                          |                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Alkylating agents          | Bendamustine (Bendeka®, Treanda®)        | Fatal and severe cases of liver injury due to confounding factors, including combination therapy, disease progression, or hepatitis B reactivation 3 months after treatment                                                                                                                                                 | Monitor LFTs prior to and during treatment.<br>No formal studies have been conducted on the impact of hepatic dysfunction on drug pharmacokinetics.<br>Avoid administration in patients with preexisting moderate to severe hepatic impairment (transaminases > 2.5 × ULN or total bilirubin > 1.5 × ULN). (Teva Pharmaceuticals, 2020)                                                                               |
|                            | Busulfan (IV: Busulfex®; oral: Myleran®) | Increased risk for SOS (AUC > 1,500 mcg × min) with 8% incidence in the setting of allogeneic HSCT; overall incidence of 7.7%–12%; jaundice, hepatic necrosis, hepatomegaly; SOS with an incidence of 20%–50% after HSCT                                                                                                    | Monitor transaminases, ALP, and bilirubin daily until day +28 post-HSCT to detect hepatotoxicity, which may indicate SOS.<br>Busulfan has not been studied in patients with hepatic dysfunction. Consider therapeutic drug monitoring with high doses. (National Institute of Diabetes and Digestive and Kidney Diseases, n.d.; Otsuka America Pharmaceutical, 2015)                                                  |
|                            | Chlorambucil (Leukeran®)                 | Jaundice, hepatotoxicity                                                                                                                                                                                                                                                                                                    | No formal studies have been conducted in patients with hepatic dysfunction. Monitor closely in patients with hepatic impairment.<br>Dose reduction may be considered, as no specific recommendations exist because of insufficient data. (GlaxoSmithKline, 2017)                                                                                                                                                      |
|                            | Cisplatin (Platinol®)                    | Increased aminotransferases, lactate dehydrogenase, and bilirubin; steatosis and cholestasis (rare)                                                                                                                                                                                                                         | Monitor LFTs. (Vicenzi et al., 2018; WG Critical Care, 2019)                                                                                                                                                                                                                                                                                                                                                          |
|                            | Cyclophosphamide (Cytoxan®)              | SOS (risk factor with a cytoreductive regimen for HSCT (10%–25%) using cyclophosphamide, total body irradiation, busulfan, or other agents; jaundice, cholestatic hepatitis, cytolytic hepatitis, hepatitis, cholestasis, hepatotoxicity with hepatic failure, hepatic encephalopathy, ascites, hepatomegaly, elevated LFTs | Dose reduction of 25% is recommended for serum bilirubin of 3.1–5 mg/dl or AST > 3 × ULN. Do not give if bilirubin > 5 mg/dl.<br>Hepatic impairment reduced conversion of the drug to the active metabolite, demonstrating possible decreased efficacy. Patients with severe hepatic dysfunction have a 40% decrease in total body clearance and 64% prolongation in elimination half-life. (Baxter Healthcare, 2013) |
|                            | Dacarbazine                              | Hepatic necrosis, hepatic vein thrombosis (0.01% incidence)                                                                                                                                                                                                                                                                 | Monitor for signs of liver toxicity. (Hospira, 2016)                                                                                                                                                                                                                                                                                                                                                                  |
|                            | Ifosfamide (Ifex®)                       | Hepatic failure, fulminant hepatitis, SOS, portal vein thrombosis, cytolytic hepatitis, cholestasis (1.8% incidence), jaundice, hepatorenal syndrome, elevated ALT/AST, ALP, gamma-glutamyl transferase, lactate dehydrogenase, and bilirubin                                                                               | Dose reduction of 25% is recommended with significant hepatic dysfunction (AST > 300 IU/L or bilirubin > 3 mg/dl).<br>No formal studies have been conducted in patients with hepatic dysfunction; use caution with administration. (Baxter Healthcare, 2018)                                                                                                                                                          |

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**TABLE 18-1.** Hepatotoxicity of Antineoplastic Agents (*Continued*)

| Classification                     | Drug                           | Side Effects                                                                                                                                                                                                                                                                                                               | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                  |
|------------------------------------|--------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Chemotherapy Agents (Cont.)</b> |                                |                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                         |
| Alkylating agents<br>(Cont.)       | Lurbinectedin (Zepzelca®)      | Increased ALT                                                                                                                                                                                                                                                                                                              | Monitor LFTs prior to initiating medication, periodically during treatment, and as clinically indicated. Withhold, reduce, or permanently discontinue drug based on severity.<br>If grade 2 events occur, withhold until $\leq$ grade 1 and resume at the same dose.<br>If $\geq$ grade 3 events occur, withhold drug until $\leq$ grade 1 and resume at the same dose.<br>(Jazz Pharmaceuticals, 2022) |
|                                    | Melphalan (Alkeran®, Evomela®) | Transient LFT abnormalities with high-dose use in HSCT, SOS (infrequent), jaundice                                                                                                                                                                                                                                         | Monitor LFTs.<br>(Spectrum Pharmaceuticals, 2017)                                                                                                                                                                                                                                                                                                                                                       |
|                                    | Oxaliplatin (Eloxatin™)        | SOS or dilatation syndrome (20%–80%); increased transaminases, ALP, and bilirubin                                                                                                                                                                                                                                          | Monitor LFTs at baseline, prior to each subsequent cycle, and as clinically indicated.<br>(Sanofi-Aventis U.S., 2020a; Vicenzi et al., 2018)                                                                                                                                                                                                                                                            |
|                                    | Temozolomide (Temodar®)        | Fatal and severe hepatotoxicity, elevated transaminases and bilirubin, cholestasis, hepatitis                                                                                                                                                                                                                              | Monitor LFTs at baseline, midway through the first cycle, prior to each subsequent cycle, and approximately 2–4 weeks after the final dose.<br>(Merck, 2015b)                                                                                                                                                                                                                                           |
|                                    | Trabectedin (Yondelis®)        | Severe hepatotoxicity, including liver failure; reported 35% incidence of grade 3–4 elevations in LFTs (1 trial); 1.3% incidence of drug-induced liver injury (ALT/AST $> 3 \times$ ULN, ALP $< 2 \times$ ULN, and bilirubin $> 2 \times$ ULN); 18% incidence of ALT/AST $> 8 \times$ ULN                                  | Monitor LFTs prior to each treatment and as clinically indicated.<br>Manage LFT elevations based on the severity of LFTs by interrupting treatment, reducing the dose, or permanently discontinuing the drug.<br>(Janssen Biotech, 2015)                                                                                                                                                                |
| Antimetabolites                    | Capecitabine (Xeloda®)         | Hyperbilirubinemia, hepatic fibrosis (0.1%), hepatitis (0.1%), cholestatic hepatitis (0.1%)                                                                                                                                                                                                                                | Hold drug for grade 3–4 elevations in bilirubin until bilirubin recovers to $< 3 \times$ ULN, then resume at 75% of starting dose for the first occurrence and 50% of starting dose for the second occurrence.<br>Discontinue drug at third occurrence.<br>(Genentech, 2015)                                                                                                                            |
|                                    | Clofarabine (Clozar®)          | Increased risk for SOS in HSCT recipients who received clofarabine in combination with other chemotherapy agents (e.g., etoposide, cyclophosphamide); severe and fatal hepatotoxicity (hepatitis and hepatic failure); elevations in AST/ALT and bilirubin within 10 days (grade 3–4), returning to grade 2 within 15 days | Monitor LFTs and for signs and symptoms of hepatitis and hepatic failure.<br>Discontinue if $\geq$ grade 3 bilirubin elevation. The drug can be restarted at a 25% dose reduction once the patient is stable and organ function is at baseline.<br>(Genzyme, 2014)                                                                                                                                      |
|                                    | Cytarabine                     | Elevated bilirubin                                                                                                                                                                                                                                                                                                         | Monitor LFTs periodically.<br>Dose reduction of 50% is recommended with any aminotransferase elevations.<br>(Hospira, 2021; Pfizer, 2011)                                                                                                                                                                                                                                                               |

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**TABLE 18-1.** Hepatotoxicity of Antineoplastic Agents (*Continued*)

| Classification                      | Drug                                           | Side Effects                                                                                                                                                                                                                                                                                                                                                                                             | Nursing Considerations                                                                                                                                                                                                                                                                                                      |
|-------------------------------------|------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Chemotherapy Agents (Cont.)</b>  |                                                |                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                             |
| Antimetabolites<br>( <i>Cont.</i> ) | 5-Fluorouracil<br>(Adrucil <sup>®</sup> )      | Transient elevations in aminotransferases associated with hepatic steatosis; rare cases of acute liver injury with jaundice                                                                                                                                                                                                                                                                              | Omit doses with liver failure (bilirubin > 5 mg/dl). No clear data exist on the monitoring of LFTs. (Spectrum Pharmaceuticals, 2016a)                                                                                                                                                                                       |
|                                     | Floxuridine<br>(FUDR <sup>®</sup> )            | Increased AST/ALT, ALP, and bilirubin; biliary sclerosis (1%–26%)                                                                                                                                                                                                                                                                                                                                        | Check LFTs at least weekly during therapy and after the drug has been discontinued if hepatotoxicity is evident. (Mayne Pharma, 2017)                                                                                                                                                                                       |
|                                     | Gemcitabine<br>(Gemzar <sup>®</sup> )          | Transient elevation in aminotransferases (up to 60%); liver failure and death (rare); increased ALP hepatic transaminitis (> 20%)                                                                                                                                                                                                                                                                        | Monitor liver function prior to starting and during treatment. Discontinue drug for severe hepatotoxicity. (Eli Lilly and Company, 2014; Vicenzi et al., 2018)                                                                                                                                                              |
|                                     | 6-Mercaptopurine<br>(Purinethol <sup>®</sup> ) | Intrahepatic cholestasis, parenchymal cell necrosis; jaundice (40%, appearing as early as 1 week or as late as 8 years after starting treatment), ascites, hepatic encephalopathy, hepatotoxicity most common when daily dose > 2 mg/kg, cholestatic liver damage and hepatocellular injury (30 days after initiation, moderate elevations in serum amino transaminases and ALP, bilirubin of 3–7 mg/dl) | Monitor LFTs prior to starting, then weekly, followed by monthly thereafter. Consider dose reduction in patients with hepatic impairment. Hold drug if signs of jaundice or hepatomegaly. Discontinue drug if LFTs continue to deteriorate and for toxic hepatitis or biliary stasis. (Nova Laboratories, 2014)             |
|                                     | Methotrexate                                   | Acute transaminitis (60%–80% in those receiving high-dose therapy, with a return to baseline in 1–2 weeks); risk for cirrhosis and fibrosis (in those receiving chronic low-dose therapy usually after > 2 years)                                                                                                                                                                                        | Obtain baseline hepatic enzyme levels prior to starting treatment, then every 1–2 months. Discontinue drug for moderate fibrosis. (Hospira, 2018)                                                                                                                                                                           |
|                                     | Nelarabine<br>(Arranon <sup>®</sup> )          | Elevated AST (6%), transaminases (12%), and bilirubin (10%) in pediatric patients                                                                                                                                                                                                                                                                                                                        | Monitor LFTs because of the risk for adverse reactions with severe hepatic impairment (total bilirubin > 3 × ULN). (GlaxoSmithKline, 2011)                                                                                                                                                                                  |
|                                     | Pemetrexed<br>(Alimta <sup>®</sup> )           | Elevated ALT/AST (8%–10%)                                                                                                                                                                                                                                                                                                                                                                                | Monitor LFTs periodically. Hold for hepatotoxicity for grade > 3, then resume upon recovery of LFTs to baseline or lower with 75% of the previous dose for bilirubin > 3 × ULN or transaminases > 5 × ULN. (Eli Lilly and Company, 2019)                                                                                    |
|                                     | Pentostatin<br>(Nipent <sup>™</sup> )          | Elevations in LFTs and hepatic disorders (2%)                                                                                                                                                                                                                                                                                                                                                            | Monitor LFTs. (Hospira, 2019)                                                                                                                                                                                                                                                                                               |
|                                     | Pralatrexate<br>(Foloty <sup>®</sup> )         | Liver abnormalities observed after drug administration                                                                                                                                                                                                                                                                                                                                                   | Monitor LFTs prior to starting the first and fourth dose of a given cycle. Consider dose modification with persistent LFT abnormalities. Do not give if bilirubin > 3–10 × ULN or transaminases > 5–20 × ULN. Discontinue treatment for bilirubin > 10 × ULN or transaminases > 20 × ULN. (Spectrum Pharmaceuticals, 2016b) |

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**TABLE 18-1.** Hepatotoxicity of Antineoplastic Agents (*Continued*)

| Classification                        | Drug                                                           | Side Effects                                                                                                                                                                                                                                                                                                                                                                                               | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                           |
|---------------------------------------|----------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Chemotherapy Agents (Cont.)</b>    |                                                                |                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Antimetabolites<br>(Cont.)            | Thioguanine<br>(Tabloid®)                                      | Jaundice; development of SOS (e.g., hyperbilirubinemia, tender hepatomegaly, weight gain due to fluid retention, ascites); portal hypertension; single case of peliosis hepatis; hepatotoxicity prevalent in men, and a high proportion in children                                                                                                                                                        | Monitor LFTs weekly upon starting, then monthly. Hold drug if toxic hepatitis or biliary stasis occurs. Discontinue drug with further hepatotoxicity, including jaundice.<br>(GlaxoSmithKline, 2012a)                                                                                                                                                                                                                            |
| Antitumor antibiotics                 | Bleomycin<br>(Blenoxane®)                                      | Transient ALT elevations associated when the drug is given in combination with other agents                                                                                                                                                                                                                                                                                                                | Effects of hepatic insufficiency on drug pharmacokinetics have not been evaluated.<br>(Nippon Kayaku, 2010)                                                                                                                                                                                                                                                                                                                      |
|                                       | Dactinomycin<br>(Cosmegen®)                                    | Transient elevations in aminotransferases; right upper quadrant pain in pediatric patients (with prior radiation therapy); hepatopathy thrombocytopenia syndrome in 1% in those treated with Wilms tumor; SOS reported, particularly in children < 48 months; ascites, hepatomegaly, hepatitis, hepatic failure with reports of death, SOS associated with a clotting disorder and multior-<br>gan failure | Assess LFTs frequently.<br>(Baxter Oncology GmbH, 2018)                                                                                                                                                                                                                                                                                                                                                                          |
|                                       | Mitomycin C<br>(Mitosol®, 3 Mito-<br>zytrex™, Mutamy-<br>cin®) | Transient ALT elevations; rare cases of SOS with high doses                                                                                                                                                                                                                                                                                                                                                | Dose adjustments from case reports include 50% dose reduction with bilirubin 1.5–3 mg/dl, 75% dose reduction with bilirubin > 3.1 mg/dl, and 50% dose reduction with bilirubin > 3 mg/dl or hepatic enzymes > 3 × ULN.<br>(Wilkes & Barton-Burke, 2020)                                                                                                                                                                          |
|                                       | Mitoxantrone<br>(Novantrone®)                                  | Increased drug concentration with severe hepatic impairment                                                                                                                                                                                                                                                                                                                                                | Monitor LFTs prior to each course of treatment. The standard dose of 14 mg/m <sup>2</sup> is recommended for moderate dysfunction (bilirubin 1.5–3.5 mg/dl), and reduction of dose to 8 mg/m <sup>2</sup> or avoidance of administration is recommended with severe hepatic impairment and bilirubin > 3.5 mg/dl. Patients with multiple sclerosis and hepatic impairment should not receive mitoxantrone.<br>(EMD Serono, 2012) |
| Antitumor antibiotics: anthracyclines | Daunorubicin<br>(Cerubidine®)                                  | May impair liver function and increase the risk of toxicity                                                                                                                                                                                                                                                                                                                                                | Dose reduction with hepatic impairment: if bilirubin is 1.2–3 mg/dl, reduce to 75% of the usual daily dose. If bilirubin > 3 mg/dl, reduce to 50% of the usual daily dose.<br>(Wilkes & Barton-Burke, 2020)                                                                                                                                                                                                                      |
|                                       | Doxorubicin<br>(Adriamycin®)                                   | Increased aminotransferases and hyperbilirubinemia                                                                                                                                                                                                                                                                                                                                                         | Monitor LFTs. Dose reduction of 50% is recommended for 1.2–3 mg/dl bilirubin, and 75% dose reduction is recommended for 3.1–5 mg/dl. Do not administer drug if bilirubin > 5 mg/dl.<br>(Pfizer, 2013)                                                                                                                                                                                                                            |

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**TABLE 18-1.** Hepatotoxicity of Antineoplastic Agents (*Continued*)

| Classification                                         | Drug                                                              | Side Effects                                                                                                                                             | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                    |
|--------------------------------------------------------|-------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Chemotherapy Agents (Cont.)</b>                     |                                                                   |                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Antitumor antibiotics: anthracyclines ( <i>Cont.</i> ) | Doxorubicin liposomal injection (Doxil <sup>®</sup> )             | Impaired liver function, hepatitis (< 1%)                                                                                                                | Monitor LFTs. Dose reduction of 50% is recommended for 1.2–3 mg/dl bilirubin, and 75% dose reduction is recommended for 3.1–5 mg/dl. Do not give if bilirubin > 5 mg/dl. (TTY Biopharm, 2019)                                                                                                                                                                                                                                             |
|                                                        | Epirubicin (Ellence <sup>®</sup> )                                | Elevated bilirubin or AST, which may delay drug clearance, increasing the risk of toxicity                                                               | Monitor bilirubin and AST before and during treatment. Avoid use in patients with hepatic impairment; no evaluations have been conducted. Dose reduction is recommended for elevated bilirubin or aminotransferase levels. If bilirubin is 1.2–3 mg/dl or AST > 2–4 × ULN, reduce dose to 50% of the recommended starting dose. If bilirubin > 3 mg/dl or AST > 4 × ULN, reduce dose to 25% of recommended starting dose. (Pfizer, 2014b) |
|                                                        | Idarubicin (Idamycin <sup>®</sup> )                               | Impaired drug metabolism caused by moderate to severe hepatic dysfunction, which may lead to elevated drug concentrations; severe hepatic changes (< 5%) | Monitor bilirubin prior to and during treatment. Drug pharmacokinetics have not been evaluated in patients with hepatic impairment. Consider dose reduction with elevated bilirubin. (Pfizer, 2014c)                                                                                                                                                                                                                                      |
| Miscellaneous                                          | Arsenic trioxide (Trisenox <sup>®</sup> )                         | Elevations in ALT/AST (> 5%)                                                                                                                             | Monitor LFTs in patients with severe hepatic impairment. (Teva Pharmaceuticals, 2015)                                                                                                                                                                                                                                                                                                                                                     |
|                                                        | L-Asparaginase (Elspar <sup>®</sup> )                             | Fulminant hepatic failure; moderate reversible elevation of aminotransferases, bilirubin, and ALP                                                        | Monitor LFTs at baseline and periodically during treatment. (Merck, 2013)                                                                                                                                                                                                                                                                                                                                                                 |
|                                                        | Asparaginase <i>Erwinia chrysanthemi</i> (Erwinaze <sup>®</sup> ) | Mild elevations in bilirubin and transaminases (4%)                                                                                                      | Monitor LFTs at baseline and periodically during treatment. (Jazz Pharmaceuticals, 2016)                                                                                                                                                                                                                                                                                                                                                  |
|                                                        | Bexarotene (Targretin <sup>®</sup> )                              | Elevations of ALT (2%–9%), AST (5%–7%), and bilirubin (0%–6%)                                                                                            | Monitor LFTs at baseline, after weeks 1, 2, and 4, and if stable, then every 8 weeks thereafter. Consider holding or discontinuing the drug if ALT/AST or bilirubin > 3 × ULN. No studies have been done in patients with hepatic insufficiency. (Valeant Pharmaceuticals North America, 2015)                                                                                                                                            |
|                                                        | Eribulin mesylate (Halaven <sup>®</sup> )                         | Grade 2 or elevated ALT (18%); elevated bilirubin; mild to moderate hepatic dysfunction (an increase of drug exposure by 1.8–2.5-fold)                   | Dose reduction is recommended in patients with hepatic dysfunction, with a dose of 1.1 mg/m <sup>2</sup> in mild (Child-Pugh A) and 0.7 mg/m <sup>2</sup> in moderate (Child-Pugh B) hepatic impairment. No studies have been conducted in patients with severe hepatic impairment. (Eisai, 2016)                                                                                                                                         |

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**TABLE 18-1.** Hepatotoxicity of Antineoplastic Agents (*Continued*)

| Classification                        | Drug                             | Side Effects                                                                                                                                                  | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|---------------------------------------|----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Chemotherapy Agents (Cont.)</b>    |                                  |                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Miscellaneous<br>( <i>Cont.</i> )     | Hydroxyurea<br>(Hydrea®)         | Elevated ALT/AST, ALP, and bilirubin                                                                                                                          | Monitor LFTs closely.<br>No specific guidance is available on dosing adjustment in patients with hepatic dysfunction.<br>(Bristol-Myers Squibb, 2016)                                                                                                                                                                                                                                                                                                                                          |
|                                       | Ixabepilone<br>(Ixempra®)        | Elevated ALT/AST and bilirubin                                                                                                                                | Monitor LFTs periodically. Recommended dosing is 40 mg/m <sup>2</sup> for bilirubin ≤ 1 × ULN and ALT/AST ≤ 2.5 × ULN, 32 mg/m <sup>2</sup> for bilirubin ≤ 1.5 × ULN and ALT/AST ≤ 10 × ULN (32 mg/m <sup>2</sup> ), and 20–30 mg/m <sup>2</sup> for bilirubin > 1.5 to ≤ 3 × ULN and ALT/AST ≤ 10 × ULN.<br>Drug is not recommended if bilirubin > 3 × ULN and ALT/AST > 10 × ULN; do not give with capecitabine if bilirubin > 2.5 × ULN and ALT/AST > ULN.<br>(Bristol-Myers Squibb, 2007) |
|                                       | Procarbazine<br>(Matulane®)      | Granulomatous hepatitis, hepatic dysfunction, jaundice                                                                                                        | Monitor LFTs prior to treatment and then at least weekly.<br>(Wilkes & Barton-Burke, 2020)                                                                                                                                                                                                                                                                                                                                                                                                     |
| Nitrosoureas                          | Carmustine<br>(BiCNU®, Gliadel®) | Increased LFTs (20%–25%, occurring as late as 4 months after treatment)                                                                                       | Monitor LFTs periodically.<br>(Heritage Pharmaceuticals, 2017)                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|                                       | Lomustine<br>(Gleostine®)        | Elevated transaminases, ALP, and bilirubin                                                                                                                    | Monitor LFTs.<br>(NextSource Biotechnology, 2016)                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                       | Streptozocin<br>(Zanosar®)       | Hepatocellular injury (15%–67%, occurring within a few days to weeks after treatment)                                                                         | Monitor LFTs during therapy.<br>(Teva Pharmaceuticals, 2012)                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Plant alkaloids: camptothecins        | Irinotecan<br>(Camptosar®)       | Elevated bilirubin (up to 25%) and aminotransferase; steatosis and steatohepatitis (25%–50%)                                                                  | Reduce dose with increased bilirubin. Do not administer in patients with bilirubin > 2 mg/dl or transaminases > 3 × ULN if no liver metastasis or transaminases > 5 × ULN with liver metastasis.<br>(Pfizer, 2014a; Vicenzi et al., 2018)                                                                                                                                                                                                                                                      |
| Plant alkaloids: epipodophyllo-toxins | Etoposide<br>(Toposar®)          | Transient elevated ALT; not usually hepatotoxic at standard dosing; SOS (risk factor with high doses or in HSCT [10%–25%]); rare severe hepatocellular damage | Monitor LFTs.<br>(Baxter Healthcare, 2017; Vicenzi et al., 2018)                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Plant alkaloids: taxanes              | Cabazitaxel<br>(Jevtana®)        | Elevated ALT/AST and bilirubin                                                                                                                                | No studies in patients with impaired liver function have been conducted. It is recommended not to give the drug if bilirubin > 3 × ULN and to dose reduce with mild to moderate hepatic dysfunction (bilirubin > ULN or AST > 1.5 × ULN).<br>The drug is not recommended in patients with hepatic impairment.<br>(Sanofi-Aventis U.S., 2010)                                                                                                                                                   |

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**TABLE 18-1.** Hepatotoxicity of Antineoplastic Agents (*Continued*)

| Classification                               | Drug                                                                                              | Side Effects                                                                                                               | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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| <b>Chemotherapy Agents (Cont.)</b>           |                                                                                                   |                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Plant alkaloids: taxanes<br>( <i>Cont.</i> ) | Docetaxel (Taxotere <sup>®</sup> )                                                                | Transient elevations in ALP, ALT/AST, and bilirubin (5%–20%); decreased clearance with elevated bilirubin or transaminases | Monitor LFTs prior to each cycle of treatment. It is recommended not to give the drug if baseline bilirubin is $> \text{ULN}$ or $\text{AST} > 1.5 \times \text{ULN}$ with $\text{ALP} > 2.5 \times \text{ULN}$ . Reduce dose by 20%–40% with grade 2–3 elevations in aminotransferases $> 2.5$ to $< 5 \times \text{ULN}$ at baseline with elevated ALP. Discontinue drug if $\text{ALT/AST} > 5 \times \text{ULN}$ or $\text{ALP} > 5 \times \text{ULN}$ . (Sanofi-Aventis U.S., 2020b)                                                                                                                                                                                         |
|                                              | Paclitaxel (Taxol <sup>®</sup> )                                                                  | Transient elevations in ALP, AST, and bilirubin (5%–20%); for high doses, up to 37%; hepatic necrosis and encephalopathy   | Monitor LFTs. Dose modifications for preexisting liver disease include a total dose of $175 \text{ mg/m}^2$ for bilirubin $\leq 1.25 \times \text{ULN}$ and $\text{AST} < 10 \times \text{ULN}$ ; a total dose of $135 \text{ mg/m}^2$ for bilirubin $1.26\text{--}2 \times \text{ULN}$ and aminotransferases $< 10 \times \text{ULN}$ ; and total dose of $90 \text{ mg/m}^2$ for bilirubin $2.01\text{--}5 \times \text{ULN}$ and aminotransferases $< 10 \times \text{ULN}$ . The drug is not recommended in patients with bilirubin $> 5\text{--}7.5 \times \text{ULN}$ or aminotransferases $\geq 10 \times \text{ULN}$ . (Bristol-Myers Squibb, 2011; Vicenzi et al., 2018) |
| Plant alkaloids: topoisomerase 1 inhibitor   | Topotecan (Hycamtin <sup>®</sup> )                                                                | Increased aminotransferases and ALP (up to 5%–8%)                                                                          | Monitor LFTs periodically prior to and during treatment. (Novartis Pharmaceuticals, 2018b; Vicenzi et al., 2018)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Plant alkaloids: vinca alkaloids             | Vincristine sulfate (Oncovin <sup>®</sup> ), Vincristine sulfate liposome (Marqibo <sup>®</sup> ) | Severe hepatotoxicity when given with irradiation; SOS, particularly in pediatric patients; elevated AST                   | Monitor LFTs. Dose reduction of 50% is recommended with bilirubin $> 3 \text{ mg/dL}$ . (Acrotech Biopharma, 2020; Hospira, 2014)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <b>Targeted Therapy Agents</b>               |                                                                                                   |                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Small molecule inhibitors                    | Afatinib (Gilotrif <sup>®</sup> )                                                                 | Liver abnormalities (10.1%) with fatal hepatic impairment (0.18%)                                                          | Monitor LFTs periodically. No dosing adjustment is recommended for mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic dysfunction. No studies have been done on severe (Child-Pugh C) hepatic dysfunction. Hold or discontinue for severe LFT changes. (Boehringer Ingelheim, 2018)                                                                                                                                                                                                                                                                                                                                                                                           |

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**TABLE 18-1.** Hepatotoxicity of Antineoplastic Agents (*Continued*)

| Classification                                | Drug                                   | Side Effects                                                                             | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
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| <b>Targeted Therapy Agents (<i>Cont.</i>)</b> |                                        |                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Small molecule inhibitors<br>( <i>Cont.</i> ) | Alectinib<br>(Alecensa <sup>®</sup> )  | Elevations of ALT > 5 × ULN (5.3%), AST > 5 × ULN (4.6%), and bilirubin > 3 × ULN (3.7%) | Monitor LFTs every 2 weeks for the first 2 months of treatment, then periodically thereafter; increase frequency with noted ALT/AST or bilirubin elevations. No dose adjustment is recommended for mild hepatic dysfunction (bilirubin ≤ ULN and AST > ULN or bilirubin 1–1.5 × ULN with any AST). For ALT/AST > 5 × ULN with bilirubin ≤ 2 × ULN, hold drug until patient recovers to baseline or ≤ 3 × ULN, and resume at dose reduction of 450 mg twice daily. For ALT/AST > 3 × ULN with bilirubin > 2 × ULN without cholestasis or hemolysis, discontinue drug. For bilirubin > 3 × ULN, hold drug until patient recovers to baseline or ≤ 1.5 × ULN, and resume at dose reduction of 450 mg twice daily. Depending on the severity of hepatic dysfunction, consider discontinuation of the drug.<br>(Genentech, 2017a) |
|                                               | Axitinib<br>(Inlyta <sup>®</sup> )     | Elevated ALT/AST more frequent than elevated ALP                                         | Monitor ALT/AST and bilirubin prior to starting treatment, then periodically throughout treatment. No dose adjustment is recommended in mild hepatic impairment (Child-Pugh A). The initial dose should be reduced by 50% in patients with moderate hepatic dysfunction (Child-Pugh B).<br>(Pfizer, 2020a)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                                               | Belinostat<br>(Beleodaq <sup>®</sup> ) | Fatal hepatotoxicity and liver abnormalities                                             | Monitor LFTs. For grade 3–4 hepatotoxicity, reduce dose by 25% (750 mg/m <sup>2</sup> ). For recurrence of grade 3–4 hepatotoxicity, after 2 dose reductions, discontinue drug.<br>(Spectrum Pharmaceuticals, 2014)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|                                               | Bortezomib<br>(Velcade <sup>®</sup> )  | Acute liver failure, hepatitis, and elevated ALT/AST and bilirubin                       | Monitor LFTs during treatment. No dosing adjustment is recommended with mild hepatic impairment (bilirubin < 1–1.5 × ULN or AST > ULN). In patients with moderate or severe hepatic dysfunction (bilirubin > 1.5–3 × ULN or bilirubin > 3 × ULN with any AST), start at a lower dose of 0.7 mg/m <sup>2</sup> for the first cycle and escalate to 1 mg/m <sup>2</sup> or reduce to 0.5 mg/m <sup>2</sup> based on tolerance.<br>(Millennium Pharmaceuticals, 2014)                                                                                                                                                                                                                                                                                                                                                           |
|                                               | Bosutinib<br>(Bosulif <sup>®</sup> )   | Elevated ALT/AST, bilirubin, and ALP                                                     | Monitor LFTs at least monthly for 3 months, then as needed. For baseline hepatic dysfunction, reduce dose to 200 mg daily. For elevated transaminases > 5 × ULN, hold drug until the patient recovers to < 2.5 × ULN and resume at 400 mg daily. Discontinue drug if recovery takes > 4 weeks. Discontinue drug if transaminases > 3 × ULN with bilirubin > 2 × ULN and ALP < 2 × ULN.<br>(Pfizer, 2017a)                                                                                                                                                                                                                                                                                                                                                                                                                    |

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**TABLE 18-1.** Hepatotoxicity of Antineoplastic Agents (*Continued*)

| Classification                                | Drug                         | Side Effects                                                                                             | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                         |
|-----------------------------------------------|------------------------------|----------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Targeted Therapy Agents (Cont.)</b>        |                              |                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                |
| Small molecule inhibitors<br>( <i>Cont.</i> ) | Cabozantinib<br>(Cabometyx®) | Elevated transaminases and bilirubin                                                                     | Reduce starting dose to 40 mg daily with mild or moderate (Child-Pugh A or B) hepatic dysfunction.<br>The drug is not recommended in patients with severe hepatic impairment.<br>(Exelixis, 2019)                                                                                                                                                                                              |
|                                               | Capmatinib<br>(Tabrecta™)    | Elevated transaminases and bilirubin                                                                     | Monitor LFTs prior to starting treatment, every 2 weeks during the first 3 months of treatment, then once a month or as clinically indicated, with more frequent testing in patients who develop increased transaminases or bilirubin. Based on the severity of the adverse reaction, withhold, dose reduce, or permanently discontinue.<br>(Novartis Pharmaceuticals, 2020)                   |
|                                               | Carfilzomib<br>(Kyprolis®)   | Hepatic failure (< 1%), elevated transaminases                                                           | Monitor LFTs regularly.<br>Consider dose reduction when appropriate.<br>(Onyx Pharmaceuticals, 2012)                                                                                                                                                                                                                                                                                           |
|                                               | Ceritinib<br>(Zykadia®)      | Elevated ALT/AST, bilirubin, and ALP                                                                     | Monitor LFTs monthly and as clinically indicated; increase frequency if elevated transaminases are noted.<br>For ALT/AST > 5 × ULN with bilirubin ≤ 2 × ULN, hold drug until patient recovers to ≤ 3 × ULN, then resume at a reduced dose of 150 mg.<br>For ALT/AST > 3 × ULN with bilirubin > 2 × ULN without cholestasis or hemolysis, discontinue drug.<br>(Novartis Pharmaceuticals, 2019) |
|                                               | Cobimetinib<br>(Cotellic®)   | Elevated transaminases and bilirubin                                                                     | Monitor LFTs before initiation of therapy, monthly during treatment, and more frequently as clinically indicated.<br>Manage grade 3–4 abnormalities with dose interruption, reduction, or discontinuation.<br>(Genentech, 2018a)                                                                                                                                                               |
|                                               | Crizotinib<br>(Xalkori®)     | Elevated ALT (grade 3–4) and bilirubin                                                                   | Monitor LFTs monthly and as clinically indicated; increase frequency in patients with grade 2–4 LFT elevations.<br>Recommend holding treatment for grade 3–4 aminotransferase elevations with bilirubin ≤ 1.5 × ULN until patient recovers to < grade 1 or baseline, then resume at 200 mg twice daily.<br>Discontinue drug for ≥ grade 2 elevated ALT/AST or bilirubin.<br>(Pfizer, 2021b)    |
|                                               | Dabrafenib<br>(Tafinlar®)    | Elevated ALT/AST, ALP, and bilirubin, when the drug used in combination with other antineoplastic agents | No formal studies have been conducted in patients with hepatic dysfunction.<br>No dose adjustment is recommended in mild hepatic impairment.<br>(GlaxoSmithKline, 2014c)                                                                                                                                                                                                                       |

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**TABLE 18-1.** Hepatotoxicity of Antineoplastic Agents (*Continued*)

| Classification                                | Drug                                                                  | Side Effects                                                                                                                                                               | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|-----------------------------------------------|-----------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Targeted Therapy Agents (Cont.)</b>        |                                                                       |                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Small molecule inhibitors<br>( <i>Cont.</i> ) | Dasatinib (Sprycel®)                                                  | Elevated transaminases and bilirubin, ascites, cholestasis, cholecystitis, hepatitis                                                                                       | Use caution with hepatic impairment. Consider holding and reducing dose with persistent elevation of ALT/AST > 5 × ULN or bilirubin > 3 × ULN. (Bristol-Myers Squibb, 2017)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                                               | Duvelisib (Copiktra®)                                                 | The median time to onset of any grade transaminase elevation was 2 months (range: 3 days to 26 months), with median event duration of 1 month (range: 1 day to 16 months). | For grade 2 ALT/AST elevation (> 3–5 × ULN), maintain dose and monitor at least weekly until return to < 3 × ULN.<br>For grade 3 ALT/AST elevation (> 5–20 × ULN), withhold and monitor at least weekly until return to < 3 × ULN. Resume at the same dose (first occurrence) or at a reduced dose for subsequent occurrence.<br>For grade 4 ALT/AST elevation (> 20 × ULN), discontinue drug. (Verastem, 2019)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|                                               | Eltrombopag (Promacta®)                                               | Increased risk of severe and potentially life-threatening hepatotoxicity                                                                                                   | Measure serum ALT, AST, and bilirubin prior to starting treatment, every 2 weeks during the dose adjustment phase, and monthly following the establishment of a stable dose.<br>Eltrombopag inhibits UGT1A1 and OATP1B1, which may lead to indirect hyperbilirubinemia. If bilirubin is elevated, perform fractionation. Evaluate abnormal serum liver tests with repeat testing within 3–5 days. If the abnormalities are confirmed, monitor serum liver tests weekly until resolved or stabilized.<br>Discontinue therapy if ALT levels ≥ 3 × ULN in patients with normal liver function or ≥ 3 × baseline (or > 5 × ULN, whichever is the lower) in patients with pre-treatment elevations in transaminases that are progressively increasing, persistent for ≥ 4 weeks, accompanied by increased direct bilirubin, or accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation.<br>If the potential benefit of reinitiating treatment outweighs the risk for hepatotoxicity, consider cautiously reintroducing therapy and measuring serum liver tests weekly during the dose adjustment phase. Hepatotoxicity may recur. (Novartis Pharmaceuticals, 2021) |
|                                               | Erlotinib (Tarceva®)                                                  | Hepatic failure and hepatorenal syndrome reported                                                                                                                          | Monitor LFTs periodically. Increase frequency with noted elevated LFTs. Closely monitor if patient has Child-Pugh A, B, or C cirrhosis.<br>Interrupt or discontinue treatment if bilirubin > 3 × ULN or elevated aminotransferases > 5 × ULN.<br>Discontinue drug with hepatic failure. (Astellas Pharma US, 2016)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                               | Everolimus (Afinitor®, Afinitor Disperz® tablets for oral suspension) | Risk for reactivation of viral hepatitis                                                                                                                                   | Dose reduction of 25% is recommended for patients with Child-Pugh A cirrhosis. A 50% reduction is recommended for Child-Pugh B cirrhosis. Dose reduction to 5 mg daily is recommended for Child-Pugh B.<br>Avoid use in patients with severe hepatic dysfunction (Child-Pugh C). (Novartis Pharmaceuticals, 2018a)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

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**TABLE 18-1.** Hepatotoxicity of Antineoplastic Agents (*Continued*)

| Classification                                | Drug                                         | Side Effects                                                                                                           | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
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| <b>Targeted Therapy Agents (Cont.)</b>        |                                              |                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Small molecule inhibitors<br>( <i>Cont.</i> ) | Fedratinib<br>(Inrebic <sup>®</sup> )        | Elevated transaminases and bilirubin                                                                                   | Monitor liver function at baseline, periodically during treatment, and as clinically indicated.<br>If $\geq$ grade ALT/AST or bilirubin, interrupt dose until resolved to $\leq$ grade 1 or baseline. Restart dose at 100 mg daily below the last given dose. Monitor ALT/AST and bilirubin (total and direct) more frequently following the dose reduction. If reoccurrence of $\geq$ grade 3, discontinue treatment.<br>(Celgene, 2019)                                                                                                                                                                                                                                                                                                                                                 |
|                                               | Gefitinib<br>(Iressa <sup>®</sup> )          | Elevated ALT/AST and bilirubin; fatal hepatotoxicity (0.04%)                                                           | Monitor LFTs periodically. Hold drug (up to 14 days) for $\geq$ grade 2 ALT/AST. Discontinue drug for severe hepatic dysfunction.<br>(AstraZeneca Pharmaceuticals, 2018)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|                                               | Idelalisib<br>(Zydelig <sup>®</sup> )        | Elevated ALT/AST (30%); fatal or serious hepatotoxicity (14%)                                                          | Monitor LFTs prior to and during treatment (every 2 weeks for first 3 months, every 4 weeks for next 3 months, then every 1–3 months thereafter). No dose adjustment is recommended for ALT/AST $> 3\text{--}5 \times \text{ULN}$ and bilirubin $> 1.5\text{--}3 \times \text{ULN}$ .<br>Monitor LFTs weekly until ALT/AST and bilirubin $\leq 1 \times \text{ULN}$ . Hold drug if ALT/AST $> 5\text{--}20 \times \text{ULN}$ and bilirubin $> 5\text{--}10 \times \text{ULN}$ . Monitor LFTs weekly until ALT/AST and bilirubin $< 1 \times \text{ULN}$ , then resume drug at dose reduction of 100 mg twice daily.<br>Discontinue drug if ALT/AST $> 20 \times \text{ULN}$ and bilirubin $> 10 \times \text{ULN}$ or if recurrent hepatotoxicity is present.<br>(Gilead Sciences, 2014) |
|                                               | Imatinib mesylate<br>(Gleevec <sup>®</sup> ) | Elevated transaminases and bilirubin (up to 10%); rare liver necrosis or failure; severe hepatotoxicity                | Monitor LFTs prior to starting treatment, monthly thereafter, and as clinically indicated. No dose adjustment is recommended with mild to moderate hepatic impairment.<br>Dose reduction by 25% is recommended for severe hepatic dysfunction. Hold for elevations of bilirubin $> 3 \times \text{ULN}$ or transaminases $> 5 \times \text{ULN}$ , then resume at reduced dosing when bilirubin $< 1.5 \times \text{ULN}$ or transaminases $< 2.5 \times \text{ULN}$ .<br>(Novartis Pharmaceuticals, 2016; Vicenzi et al., 2018)                                                                                                                                                                                                                                                          |
|                                               | Ixazomib<br>(Ninlaro <sup>®</sup> )          | Drug-induced liver injury, hepatocellular injury, hepatic steatosis, hepatitis cholestasis, hepatotoxicity ( $< 1\%$ ) | Monitor LFTs during treatment.<br>Dose reduction of starting dose to 3 mg is recommended in moderate to severe (total bilirubin $> 1.5\text{--}3 \times \text{ULN}$ ) or severe (total bilirubin $> 3 \times \text{ULN}$ ) hepatic impairment.<br>(Millennium Pharmaceuticals, 2015)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

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**TABLE 18-1.** Hepatotoxicity of Antineoplastic Agents (*Continued*)

| Classification                                | Drug                                    | Side Effects                                                                 | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|-----------------------------------------------|-----------------------------------------|------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Targeted Therapy Agents (<i>Cont.</i>)</b> |                                         |                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Small molecule inhibitors<br>( <i>Cont.</i> ) | Lapatinib<br>(Tykerb <sup>®</sup> )     | Elevated ALT/AST and bilirubin (< 1%)                                        | Monitor LFTs prior to starting treatment, every 4–6 weeks during therapy, then as clinically indicated.<br>Discontinue drug for severe changes in LFTs (ALT/AST > 3 × ULN, bilirubin > 2 × ULN).<br>(GlaxoSmithKline, 2018)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                                               | Lenvatinib<br>(Lenvima <sup>®</sup> )   | Elevated ALT/AST                                                             | Monitor LFTs prior to starting treatment, every 2 weeks for the first 2 months, and at least monthly thereafter during therapy. No dose adjustment is recommended for mild to moderate hepatic dysfunction.<br>Hold drug for ≥ grade 3 hepatic impairment.<br>Dose reduction to 14 mg daily is recommended for severe (Child-Pugh C) hepatic dysfunction.<br>Discontinue drug for hepatic failure.<br>(Eisai, 2018)                                                                                                                                                                                                                                                                                           |
|                                               | Lorlatinib<br>(Lorbrena <sup>®</sup> )  | Risk of serious hepatotoxicity with concomitant use of strong CYP3A inducers | Discontinue strong CYP3A inducers for 3 plasma half-lives of the strong CYP3A inducer prior to starting treatment.<br>(Pfizer, 2021a)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                               | Nilotinib<br>(Tasigna <sup>®</sup> )    | Elevated ALT/AST, bilirubin, and ALP                                         | Monitor LFTs periodically. Hold drug for elevated bilirubin or transaminases ≥ grade 3 until patient recovers to ≤ grade 1. Resume drug at dose reduction of 400 mg daily.<br>(Novartis Pharmaceuticals, 2010)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                               | Panobinostat<br>(Farydak <sup>®</sup> ) | Elevated transaminases and bilirubin                                         | Monitor LFTs prior to and regularly during treatment.<br>Dose reduction is recommended for mild hepatic impairment (starting dose 15 mg) and moderate hepatic impairment (10 mg).<br>Avoid use in severe hepatic dysfunction.<br>(Novartis Pharmaceuticals, 2015)                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|                                               | Pazopanib<br>(Votrient <sup>®</sup> )   | Elevated transaminases and bilirubin; fatal hepatotoxicity                   | Monitor LFTs prior to starting, at least once every 4 weeks for the first 4 months or as clinically indicated, and periodically after therapy.<br>No dose adjustment is recommended for isolated ALT > 3–8 × ULN; check weekly LFTs until the patient recovers to < grade 1 or baseline.<br>Hold drug for isolated ALT > 8 × ULN until patient recovers to < grade 1 or baseline. Consider resuming the drug at dose reduction to no greater than 400 mg daily. Check LFTs weekly for 8 weeks; discontinue drug if elevated ALT > 3 × ULN recurs or if ALT > 3 × ULN with bilirubin > 2 × ULN occurs.<br>The drug is not recommended for patients with severe hepatic impairment.<br>(GlaxoSmithKline, 2012b) |

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**TABLE 18-1.** Hepatotoxicity of Antineoplastic Agents (*Continued*)

| Classification                                | Drug                       | Side Effects                                                                                                                    | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|-----------------------------------------------|----------------------------|---------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Targeted Therapy Agents (Cont.)</b>        |                            |                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Small molecule inhibitors<br>( <i>Cont.</i> ) | Pexidartinib<br>(Turalio™) | Serious and potentially fatal liver injury; only available through a restricted risk evaluation and mitigation strategy program | Taking with food increases drug exposure by 100% and may increase the risk of hepatotoxicity. Administer on an empty stomach, either 1 hour before or 2 hours after a meal or snack.<br>Monitor LFTs prior to starting treatment, weekly for the first 8 weeks, every 2 weeks for the next month, and every 3 months thereafter. Withhold and dose reduce, or permanently discontinue based on the severity of the hepatotoxicity. Rechallenge with a reduced dose may result in a recurrence of increased serum transaminases, bilirubin, or ALP. Monitor LFTs weekly for the first month after rechallenge.<br>(Daiichi Sankyo, 2020)   |
|                                               | Ponatinib<br>(Iclusig®)    | Elevated ALT/AST                                                                                                                | Monitor LFTs prior to, monthly, and as clinically indicated during treatment. Hold drug with elevation of transaminases $> 3 \times \text{ULN}$ ( $\geq$ grade 2) until patient recovers to $< 3 \times \text{ULN}$ (grade 1), then resume drug at a reduced dose. Discontinue drug with elevations of ALT/AST $> 3 \times \text{ULN}$ with elevated bilirubin $> 2 \times \text{ULN}$ and ALP $< 2 \times \text{ULN}$ .<br>Avoid giving the drug in patients with moderate to severe (Child-Pugh B or C) hepatic dysfunction.<br>(ARIAD Pharmaceuticals, 2016)                                                                           |
|                                               | Pralsetinib<br>(Gavreto™)  | Elevated transaminases                                                                                                          | Monitor ALT/AST prior to starting treatment, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose, or permanently discontinue drug based on severity (Genentech, 2021).                                                                                                                                                                                                                                                                                                                                                                                                    |
|                                               | Regorafenib<br>(Stivarga®) | Elevated LFTs; hepatocellular necrosis                                                                                          | Obtain baseline LFTs prior to starting treatment, at least every 2 weeks during the first 2 months of treatment, then monthly.<br>Dose reduction is recommended for grade 2 hepatic impairment.<br>Discontinue drug for ALT/AST $> 20 \times \text{ULN}$ or ALT/AST $> 3 \times \text{ULN}$ with bilirubin $> 2 \times \text{ULN}$ or recurrence of ALT/AST $> 5 \times \text{ULN}$ despite dose reduction.<br>Drug is not recommended for patients with severe hepatic impairment (Child-Pugh C).<br>(Bayer HealthCare Pharmaceuticals, 2020)                                                                                            |
|                                               | Ribociclib<br>(Kisqali®)   | Elevated ALT/AST (7%–10%; grade 3–4) and bilirubin (1%)                                                                         | Monitor LFTs at baseline, every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles, then as clinically indicated.<br>Dose reduce to 400 mg in patients with moderate to severe hepatic impairment (Child-Pugh B or C).<br>Hold for ALT/AST $> 3\text{--}20 \times \text{ULN}$ until patient recovers to baseline or $<$ grade 2–3 toxicity. Consider resuming at the same dose or reducing the dose depending on toxicity.<br>Discontinue drug for elevated ALT/AST $> 3 \times \text{ULN}$ with bilirubin $> 2 \times \text{ULN}$ or if ALT/AST $> 20 \times \text{ULN}$ .<br>(Novartis Pharmaceuticals, 2017) |

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**TABLE 18-1.** Hepatotoxicity of Antineoplastic Agents (*Continued*)

| Classification                                | Drug                                    | Side Effects                                   | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|-----------------------------------------------|-----------------------------------------|------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Targeted Therapy Agents (<i>Cont.</i>)</b> |                                         |                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Small molecule inhibitors<br>( <i>Cont.</i> ) | Sorafenib<br>(Nexavar <sup>®</sup> )    | Elevated transaminases and bilirubin           | Monitor LFTs regularly.<br>Discontinue drug if transaminases are significantly increased without other etiology.<br>No dosing adjustment is recommended for Child-Pugh A or B hepatic impairment.<br>(Bayer HealthCare Pharmaceuticals, 2018)                                                                                                                                                                                                                                                                                                 |
|                                               | Sotorasib<br>(Lumakras <sup>™</sup> )   | Elevated transaminases and bilirubin           | Monitor LFTs every 3 weeks for the first 3 months of treatment, then once monthly as clinically indicated. Withhold, reduce dose, or permanently discontinue drug based on the severity.<br>(Amgen, 2021)                                                                                                                                                                                                                                                                                                                                     |
|                                               | Sunitinib<br>(Sutent <sup>®</sup> )     | Jaundice; elevated transaminases and bilirubin | Monitor LFTs prior to starting treatment, during each cycle, and as clinically indicated.<br>Hold drug for grade 3–4 drug-related hepatic adverse events.<br>Discontinue drug if the patient has no resolution, experiences severe changes in LFTs after stopping the drug, or has other signs or symptoms of liver failure.<br>Safety with ALT/AST > 2.5 × ULN, or ALT/AST > 5 × ULN if due to liver metastases has not been established.<br>No dose adjustment is recommended with Child-Pugh A or B hepatic impairment.<br>(Pfizer, 2017b) |
|                                               | Temsirolimus<br>(Torisel <sup>®</sup> ) | Elevated ALT, ALP, and bilirubin               | Monitor LFTs.<br>Dose reduction to 15 mg weekly is recommended for mild hepatic impairment (bilirubin > 1–1.5 × ULN or AST > ULN).<br>Do not give drug if bilirubin > 1.5 × ULN.<br>(Pfizer, 2017c)                                                                                                                                                                                                                                                                                                                                           |
|                                               | Trametinib<br>(Mekinist <sup>®</sup> )  | Elevated ALT/AST and ALP                       | Baseline and periodic monitoring of LFTs are recommended.<br>No dose adjustment is recommended for mild hepatic impairment.<br>(GlaxoSmithKline, 2014b)                                                                                                                                                                                                                                                                                                                                                                                       |
|                                               | Tucatinib<br>(Tukysa <sup>®</sup> )     | Elevated transaminases and bilirubin           | For patients with severe hepatic impairment (Child-Pugh C), reduce the recommended dose to 200 mg PO twice daily.<br>Monitor ALT, AST, and bilirubin prior to starting, every 3 weeks during treatment, and as clinically indicated. Based on the severity of hepatotoxicity, interrupt dose then dose reduce or permanently discontinue.<br>(Seagen, 2020)                                                                                                                                                                                   |

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**TABLE 18-1.** Hepatotoxicity of Antineoplastic Agents (*Continued*)

| Classification                                          | Drug                      | Side Effects                                                                                                                                                                                   | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|---------------------------------------------------------|---------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Targeted Therapy Agents (Cont.)</b>                  |                           |                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Small molecule inhibitors<br>( <i>Cont.</i> )           | Umbralisib (Ukoniq™)      | Elevated transaminases                                                                                                                                                                         | Monitor liver function at baseline and during treatment. For ALT/AST greater than 5 to less than 20 × ULN, withhold until return to < 3 × ULN, then resume at a reduced dose. For ALT/AST elevation > 20 × ULN, discontinue drug. (TG Therapeutics, 2021)                                                                                                                                                                                                                                                                                                                                                    |
|                                                         | Vandetanib (Caprelsa®)    | Elevated ALT/AST (20%) and bilirubin                                                                                                                                                           | Dose reduction is recommended for ≥ grade 3 toxicity. The drug is not recommended in patients with moderate or severe hepatic impairment. It is recommended to avoid use in patients with severe hepatic impairment (Child-Pugh B or C cirrhosis). (AstraZeneca Pharmaceuticals, 2014)                                                                                                                                                                                                                                                                                                                       |
|                                                         | Vemurafenib (Zelboraf®)   | Elevated ALT/AST, ALP, and bilirubin                                                                                                                                                           | Monitor LFTs prior to starting therapy and monthly during therapy or as clinically indicated. Hold drug for grade 2–3 toxicities until patient recovers to < grade 1 toxicity or baseline. Resume at recommended dose reductions. Discontinue drug for grade 4 toxicities. (Genentech, 2017c)                                                                                                                                                                                                                                                                                                                |
| <b>Immunotherapy Agents</b>                             |                           |                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Checkpoint inhibitors: cytotoxic T-lymphocyte antigen 4 | Ipilimumab (Yervoy®)      | Immune-related hepatitis T-cell activation and proliferation, leading to immune-mediated organ failure, increased aminotransferases, and hyperbilirubinemia                                    | Monitor LFTs and assess for signs and symptoms of hepatotoxicity prior to each dose. No dose adjustment is recommended for mild hepatic dysfunction (bilirubin > 1–1.5 × ULN or ALT/AST > ULN). Hold drug for grade 2 toxicities. Discontinue drug for grade 3–4 toxicities; initiate steroids (1–2 mg/kg prednisone daily or equivalent) until LFTs return to baseline or evidence of sustained improvement is seen. Taper steroids over 1 month. Mycophenolate has been given in the setting of persistent severe hepatitis despite high-dose steroids. (Bristol-Myers Squibb, 2020; Vicenzi et al., 2018) |
| Checkpoint inhibitors: programmed cell death protein 1  | Nivolumab (Opdivo®)       | Elevated ALT (16%), AST (28%), ALP (22%), and bilirubin (9%); immune-mediated hepatitis (1.1%)                                                                                                 | Monitor LFTs prior to and periodically during treatment. For ≥ grade 2 elevations in transaminases or bilirubin, initiate steroids 1–2 mg/kg prednisone daily or equivalent. Discontinue drug for grade 3–4 hepatitis. (Bristol-Myers Squibb, 2021)                                                                                                                                                                                                                                                                                                                                                          |
|                                                         | Pembrolizumab (Keytruda®) | Immune-mediated hepatitis (0.7%; grade 2: 0.1%; grade 3: 0.4%; grade 4: < 0.1%), elevated ALP (26%; grade 3–4: 3.1%), elevated AST (22%; grade 3–4: 2.1%), elevated ALT (21%; grade 3–4: 1.8%) | Monitor for LFT changes. For grade 2 LFT changes, initiate steroids 0.5–1 mg/kg daily; for ≥ grade 3, initiate steroids 1–2 mg/kg prednisone daily or equivalent followed by a taper. Depending on severity of LFT changes, hold or discontinue drug. (Merck, 2021)                                                                                                                                                                                                                                                                                                                                          |

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**TABLE 18-1.** Hepatotoxicity of Antineoplastic Agents (*Continued*)

| Classification                                        | Drug                      | Side Effects                                                                                                                                                                                                                                                                                                                                   | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|-------------------------------------------------------|---------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Immunotherapy Agents (Cont.)</b>                   |                           |                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Checkpoint inhibitors: programmed cell death-ligand 1 | Atezolizumab (Tecentriq®) | Across clinical trials (N = 1,978): grade 3–4 elevations in ALT (2.5%), AST (2.3%), and total bilirubin (1.6%); in patients with urothelial carcinoma (n = 523): immune-mediated hepatitis (1.3%), grade 3–4 elevations in ALT (2.5%), AST (2.5%), and total bilirubin (2.1%), with median time to onset of 1.1 months (range: 0.4–7.7 months) | Monitor for LFT changes, including signs and symptoms of hepatitis. Monitor AST, ALT, and bilirubin prior to and periodically during treatment. Administer corticosteroids at dose of 1–2 mg/kg prednisone daily equivalents for ≥ grade 2 transaminase elevations, with or without concurrent total bilirubin elevation, followed by corticosteroid taper. Hold drug for moderate hepatic impairment (ALT or AST > 3–5 × ULN or total bilirubin > 1.5–3 × ULN). Permanently discontinue drug for severe or life-threatening hepatic impairment (AST or ALT > 5 × ULN or total bilirubin > 3 × ULN). (Genentech, 2018b)                                                    |
|                                                       | Avelumab (Bavencio®)      | Immune-mediated hepatitis (0.9%; grade 3: 0.6%; grade 5: 0.1%; median time to onset 3.2 months [range 1 week to 15 months]; median duration 2.5 months [range 1 day to 7+ months]); grade 3–4 elevations in AST (1%), ALT (5%), and total bilirubin (1%)                                                                                       | Monitor patients for abnormal LFTs prior to and periodically during treatment. Administer corticosteroids (initial dose of 1–2 mg/kg prednisone daily or equivalent, followed by a corticosteroid taper) for ≥ grade 2 hepatitis. Withhold drug for moderate (grade 2; AST/ALT 3–5 × ULN or total bilirubin > 1.5 and up to 3 × ULN) or immune-mediated hepatitis until resolution, and permanently discontinue for severe (grade 3 ALT/AST > 5 × ULN or total bilirubin > 3 × ULN) or life-threatening (grade 4) immune-mediated hepatitis. (EMD Serono & Pfizer, 2019)                                                                                                   |
|                                                       | Durvalumab (Imfinzi®)     | Immune-mediated hepatitis (1.1%; grade 3: 0.6%; median time to onset of 51.5 days [range: 15–312 days]); grade 3–4 elevations in ALT (3%), AST (4.3%), and total bilirubin (2.8%)                                                                                                                                                              | Monitor LFTs for changes in each cycle during treatment. For grade 2–3 elevations in transaminases with or without concurrent total bilirubin elevation, initiate dose of 1–2 mg/kg prednisone daily or equivalent followed by taper. Hold drug for moderate hepatic impairment (grade 2 ALT/AST > 3–5 × ULN or total bilirubin > 1.5–3 × ULN; grade 3 ALT/AST ≤ 8 × ULN or total bilirubin ≤ 5 × ULN). Permanently discontinue drug for severe or life-threatening hepatic impairment (grade 3 ALT or AST > 8 × ULN or total bilirubin > 5 × ULN; concurrent ALT or AST > 3 × ULN and total bilirubin > 2 × ULN with no other cause). (AstraZeneca Pharmaceuticals, 2020) |
|                                                       | Cemiplimab (Libtayo®)     | Immune-mediated hepatitis (2.1%); grade 3 (1.7%), grade 4–5 (0.2%); grade 3 AST (3%)                                                                                                                                                                                                                                                           | Withhold drug if ALT/AST increases to > 3–10 × ULN or if total bilirubin increases up to 3 × ULN. Permanently discontinue drug if AST/ALT increases to > 10 × ULN or total bilirubin increases to > 3 × ULN. Systemic corticosteroids were required in all patients with hepatitis, including 91% who received prednisone ≥ 40 mg daily or equivalent. (Morgado et al., 2020; Regeneron Pharmaceuticals, 2021)                                                                                                                                                                                                                                                             |

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**TABLE 18-1.** Hepatotoxicity of Antineoplastic Agents (*Continued*)

| Classification                                                | Drug                                                                              | Side Effects                                                                                                                                                                                                                                                                                                                                                                            | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|---------------------------------------------------------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Immunotherapy Agents (Cont.)</b>                           |                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Cytokines: interferons                                        | Pegylated interferon alfa-2a (Pegasys®); pegylated interferon alfa-2b (Sylatron™) | Significant elevation in aminotransferases ( $> 10 \times \text{ULN}$ )                                                                                                                                                                                                                                                                                                                 | Monitor LFTs on weeks 1, 2, 4, 6, and 8; then every 4–6 weeks; and more frequently if abnormalities. It is recommended to hold dose if aminotransferases $> 5 \times \text{ULN}$ until resolution to grade 1, then reduce dose by 33%. (Hoffmann-La Roche, 2011; Merck, 2015a)                                                                                                                                                                                                                                                                                  |
| Cytokines: interleukins                                       | Interleukin-2, aldesleukin (Proleukin®)                                           | Hepatitis, hepatosplenomegaly, cholecystitis                                                                                                                                                                                                                                                                                                                                            | Monitor LFTs prior to starting therapy, then daily during treatment. (Bayer HealthCare Pharmaceuticals, 2012)                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Interleukin-3 receptor alpha chain (CD123)-directed cytotoxin | Tagraxofusp-erzs (Elzonris™)                                                      | Hepatotoxicity                                                                                                                                                                                                                                                                                                                                                                          | Monitor ALT/AST prior to each infusion. Withhold therapy if ALT/AST increases $> 5 \times \text{ULN}$ . Treatment can resume when transaminase elevations are $\leq 2.5 \times \text{ULN}$ . (Stemline Therapeutics, 2018)                                                                                                                                                                                                                                                                                                                                      |
| Immunomodulators                                              | Lenalidomide (Revlimid®)                                                          | Hepatic failure, including fatalities (15% with hepatocellular, cholestatic, and mixed characteristic); patients with multiple myeloma (2%) and myelodysplasia (1%) with hepatotoxicity events (e.g., hyperbilirubinemia, cholecystitis, acute cholecystitis, hepatic failure); risk factors: preexisting viral liver disease, elevated baseline liver enzymes, concomitant medications | Monitor LFTs periodically; stop drug and evaluate if hepatotoxicity is suspected. Treatment at lower dose may be considered if LFTs return to baseline values. (Celgene, 2013)                                                                                                                                                                                                                                                                                                                                                                                  |
|                                                               | Pomalidomide (Pomalyst®)                                                          | Elevated bilirubin                                                                                                                                                                                                                                                                                                                                                                      | Avoid in patients with bilirubin $> 2 \text{ mg/dl}$ or ALT/AST $> 3 \times \text{ULN}$ . Dose reduction of 25% is recommended for mild or moderate (Child-Pugh A or B) hepatic impairment; 50% dose reduction is recommended for severe (Child-Pugh C) hepatic impairment. (Celgene, 2017)                                                                                                                                                                                                                                                                     |
|                                                               | Thalidomide (Thalomid®)                                                           | Elevated ALP and bilirubinemia                                                                                                                                                                                                                                                                                                                                                          | No pharmacokinetic studies have been conducted in patients with hepatic impairment. (Celgene, 2014)                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Monoclonal antibodies: human                                  | Ado-trastuzumab emtansine (Kadcyla®)                                              | Mixed pattern of elevated ALP, ALT/AST, and bilirubin                                                                                                                                                                                                                                                                                                                                   | Monitor LFTs prior to starting therapy and before each dose. Clinical trials excluded patients with known active hepatitis B or C infection, baseline transaminases $> 2.5 \times \text{ULN}$ , or bilirubin $> 1.5 \times \text{ULN}$ (treat at same dose level of 3.6 mg/kg). Hold for grade 3 ( $> 5\text{--}20 \times \text{ULN}$ ) elevations in ALT/AST or grade 2–3 ( $> 1.5\text{--}10 \times \text{ULN}$ ) elevations in bilirubin; resume at one lower dose level only if ALT/AST recover to $\leq$ grade 2 and bilirubin recovers to $\leq$ grade 1. |

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**TABLE 18-1.** Hepatotoxicity of Antineoplastic Agents (*Continued*)

| Classification                          | Drug                                            | Side Effects                                                                                           | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|-----------------------------------------|-------------------------------------------------|--------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Immunotherapy Agents (Cont.)</b>     |                                                 |                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Monoclonal antibodies: human<br>(Cont.) | Ado-trastuzumab emtansine (Kadcyla®)<br>(Cont.) |                                                                                                        | Discontinue if hepatotoxicity recurs when restarting drug or if grade 4 increased transaminases (ALT/AST > 20 × ULN) or hyperbilirubinemia (bilirubin > 10 × ULN) occurs at any time during treatment.<br>Discontinue if ALT/AST > 3 × ULN with bilirubin > 2 × ULN.<br>(Genentech, 2019)                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Monoclonal antibodies: humanized        | Alemtuzumab (Campath®, Lemtrada®)               | Risk of hepatitis B and C reactivation; intrinsic hepatotoxicity and idiosyncratic liver injury (rare) | Screen for hepatitis B and C prior to starting treatment.<br>Provide prophylaxis or treatment of hepatitis B and C before or during treatment.<br>(Genzyme, 2007)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|                                         | Brentuximab (Adcetris®)                         | Severe and potentially fatal hepatotoxicity, including elevated transaminases and bilirubin            | Monitor LFTs.<br>Avoid drug with Child-Pugh B or C hepatic impairment.<br>(Seattle Genetics, 2014)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                                         | Elotuzumab (Empliciti™)                         | ALT/AST > 3 × ULN, bilirubin > 2 × ULN, ALP < 2 × ULN                                                  | Monitor LFTs periodically.<br>Recommend periodic monitoring of liver enzymes; temporarily discontinue drug for ≥ grade 3 hepatotoxicity.<br>(Bristol-Myers Squibb, 2019)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|                                         | Gemtuzumab ozogamicin (Mylotarg™)               | Hepatotoxicity, including severe or fatal SOS                                                          | Assess ALT/AST, total bilirubin, and ALP prior to each dose.<br>After treatment, monitor frequently for signs and symptoms of SOS, including elevations in ALT/AST, total bilirubin, hepatomegaly (which may be painful), rapid weight gain, and ascites.<br>For patients who develop abnormal LFTs, more frequent monitoring of LFTs and clinical signs and symptoms of hepatotoxicity is recommended.<br>For patients who proceed to HSCT, monitor LFTs frequently during the post-HSCT period, as appropriate.<br>Manage signs or symptoms of hepatotoxicity by medication dose interruption or discontinuation.<br>For patients who experience SOS, discontinue and treat according to standard medical practice.<br>(Wyeth Pharmaceuticals, 2021) |
|                                         | Inotuzumab ozogamicin (Besponsa®)               | Hepatotoxicity, including SOS (life-threatening with increased risk in HSCT recipients)                | Monitor LFTs prior to and following each dose.<br>No adjustment to starting dose is required if total bilirubin ≤ 1.5 × ULN and AST/ALT ≤ 2.5 × ULN.<br>Interrupt drug if total bilirubin > 1.5 × ULN and AST/ALT > 2.5 × ULN.<br>Permanently discontinue drug if SOS or severe liver toxicity occurs or if LFTs do not recover to baseline.<br>(Wyeth Pharmaceuticals, 2017)                                                                                                                                                                                                                                                                                                                                                                          |

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**TABLE 18-1.** Hepatotoxicity of Antineoplastic Agents (*Continued*)

| Classification                                    | Drug                                            | Side Effects                                                                                                                     | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|---------------------------------------------------|-------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Immunotherapy Agents (Cont.)</b>               |                                                 |                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Monoclonal antibodies: humanized ( <i>Cont.</i> ) | Obinutuzumab (Gazyva <sup>®</sup> )             | Hepatitis B virus reactivation, with some cases resulting in fulminant hepatitis, hepatic failure, and death                     | Screen for hepatitis B infection (hepatitis B surface antigen and hepatitis B core antibody) prior to starting treatment; if patient is positive for hepatitis B infection, consult expert for monitoring and consideration of antiviral therapy. Monitor patients with current or prior hepatitis B infection for signs of hepatitis or hepatitis B reactivation during therapy and for several months after treatment. Discontinue drug for hepatitis B reactivation while on treatment. Insufficient data exist on safety of resuming drug in patients with hepatitis B reactivation. (Genentech, 2017b)                                                                                                                     |
|                                                   | Ofatumumab (Arzerra <sup>®</sup> )              | Hepatitis B virus reactivation, fulminant hepatitis                                                                              | Screen high-risk patients prior to starting treatment. Monitor carriers of hepatitis B closely for clinical and laboratory signs of active infection during treatment and for 6–12 months following final dose. Discontinue drug in patients who develop viral hepatitis or viral hepatitis reactivation. (GlaxoSmithKline, 2014a)                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                   | Polatuzumab vedotin-piiq (Polivy <sup>™</sup> ) | Preexisting liver disease, elevated baseline liver enzymes, and concomitant medications that increase the risk of hepatotoxicity | Monitor liver enzymes and bilirubin levels. (Genentech, 2020)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Hormone Therapy Agents</b>                     |                                                 |                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Androgen inhibitor                                | Abiraterone acetate (Zytiga <sup>®</sup> )      | Elevated ALT/AST and bilirubin                                                                                                   | Monitor ALT/AST and bilirubin prior to starting therapy, every week for the first month, every 2 weeks for the following 2 months of treatment, then monthly thereafter. For moderate hepatic impairment, reduce dose to 250 mg daily. Hold drug if ALT/AST > 5 × ULN or bilirubin > 3 × ULN until patient recovers to baseline or ALT/AST ≤ 2.5 × ULN or bilirubin ≤ 1.5 × ULN. Resume at reduced dose of 750 mg daily at first occurrence and 500 mg daily at second occurrence. Discontinue if ALT/AST > 5 × ULN or bilirubin > 3 × ULN with moderate hepatic impairment or if the patient is unable to tolerate 500 mg daily. Avoid drug in patients with severe hepatic impairment (Child-Pugh C). (Janssen Biotech, 2020) |

*Note.* Review package inserts for dosing and prescribing information.

ALP—alkaline phosphatase; ALT—alanine aminotransferase; AST—aspartate aminotransferase; AUC—area under the plasma concentration versus-time curve; HSCT—hematopoietic stem cell transplantation; LFTs—liver function tests; SOS—sinusoidal obstruction syndrome; ULN—upper limit of normal

- a) Malaise, myalgia, arthralgia, low-grade fever
  - b) Gastrointestinal symptoms (e.g., anorexia, nausea, vomiting, right upper quadrant pain, acholic stools that are pale, clay-like, or putty-colored due to problems in the biliary system)
  - c) Jaundice, hyperpigmentation, ascites
  - d) Dark-colored urine
  - e) Pruritus
  - f) Hepatomegaly
  - g) Coagulopathy; bruising or bleeding
  - h) Hepatic encephalopathy
  - i) Hypersensitivity reactions (e.g., fever, rash, mononucleosis illness, additional evidence of toxicity to other organs)
- F. Pathologic manifestations associated with drug toxicity in the liver (Botti et al., 2016; Gordon et al., 2017; Mehta, 2019; Tewari et al., 2017)
1. Acute hepatocellular injury
    - a) Incidence: 90% of cases (Mehta, 2019)
    - b) Pathophysiology
      - (1) Hepatocellular apoptosis, steatosis, or cellular degeneration can occur.
      - (2) Liver cells appear spotty (minute clusters of hepatocytes) or confluent (larger groups of hepatocytes involving multiple lobules under microscopy) (Krishna, 2017).
      - (3) The hepatic acinus is the functional unit in the liver that is divided into different zones.
        - (a) Zone 1 encircles the portal tracts, where oxygenated blood from hepatic arteries enters. Zone 3 is located around the central veins, where oxygenation is poor. Zone 2 is located between zones 1 and 3.
        - (b) Zone 3 is most commonly affected.
          - i. Zonal necrosis occurs with compounds with predictable, dose-dependent, and intrinsic toxicity.
          - ii. Nonzonal necrosis (diffuse, irregular, patchy injury involving all parts of the acinus) occurs with compounds with unpredictable idiosyncratic injury (Fisher et al., 2015).
      - (4) Most recover without developing significant fibrosis.
    - c) Signs and symptoms include jaundice, painful hepatomegaly, abdominal distension, nausea and vomiting, malaise, confusion, and sleepiness.
  2. Chronic hepatocellular injury
    - a) Incidence: 5%–10% of cases (Mehta, 2019)
    - b) Pathophysiology
      - (1) Pigment accumulation (excessive iron): Lipofuscin (fine yellow-brown pigment granules) is found in hepatic cells as a result of certain drugs. Excessive iron may accumulate in the liver due to over ingestion or parenteral therapy (Mehta, 2019).
      - (2) Steatosis, steatohepatitis, phospholipidosis
      - (3) Hepatic fibrosis, cirrhosis
    - c) Signs and symptoms include nausea, diarrhea, poor appetite, weight loss, fatigue, jaundice, easy bruising or bleeding, pruritus, and lower extremity swelling.
  3. Acute cholestasis: decrease in bile flow due to impaired secretion by hepatocytes or bile flow obstruction through intra- or extrahepatic bile ducts (Gasmi & Kleiner, 2020; Mehta, 2019; Nazer, 2017)
    - a) Incidence: 2%–5% of cases (Mehta, 2019)
    - b) Pathophysiology (Gasmi & Kleiner, 2020; Mehta, 2019; Nazer, 2017)
      - (1) Reduction in bile flow due to decreased secretion or biliary tree obstruction
      - (2) Pure cholestasis (canalicular, bland, or noninflammatory) characterized by prominent hepatocellular or canalicular cholestasis with minimal hepatocellular injury or inflammation
      - (3) Cholestatic hepatitis (hepatocanalicular, cholangiolitic, or inflammatory) characterized by inflammation, prominent cholestasis, and hepatocellular injury
    - c) Signs and symptoms include pruritus, jaundice, pale stools, and dark urine.
  4. Chronic cholestasis
    - a) Incidence
      - (1) Approximately 1% of cases
      - (2) Progresses to cirrhosis in rare cases (Mehta, 2019)
    - b) Pathophysiology (Mehta, 2019)
      - (1) Bile duct loss or cholate stasis (the rim of pale hepatocytes adjacent to portal tracts)
      - (2) Prolonged damage leading to bile duct loss and overt ductopenia
    - c) Signs and symptoms include pruritus, jaundice, pale stools, and dark urine.
  5. Steatosis: infiltration of liver cells with fat, which is associated with metabolism being disturbed by drug therapy and mitochondrial function (Mehta, 2019; Meunier & Larrey, 2020)
    - a) Incidence: 20%–30% of cases (Meunier & Larrey, 2020)
    - b) Pathophysiology
      - (1) Acute steatosis causes hepatic cells to appear microvesicular (small vesicles of fat droplets). In contrast, chronic steatosis causes hepatic cells to appear macrovesic-

- ular (large vesicles of fat droplets) under microscopy (Gasmi & Kleiner, 2020).
- (2) Hepatocytes are filled with excess fatty cells composed of triglycerides (Marchisello et al., 2019).
- (3) Disruption occurs in mitochondrial beta-oxidation of lipids.
- (4) Steatohepatitis includes variable steatosis, lobular inflammation, and hepatocellular injury.
- c) Signs and symptoms include ascites, jaundice, confusion, and tendency to bleed easily.
- 6. Granulomas: macrophages that have accumulated in the liver because of chronic exposure to drug therapy (Culver et al., 2016; Mehta, 2019)
  - a) Incidence: 2%–15% of cases (Ortiz-Brizuela et al., 2019)
  - b) Pathophysiology
    - (1) Inflammatory process
    - (2) Seen in periportal and portal areas
    - (3) Temporary injury
  - c) Signs and symptoms include fevers, myalgias, fatigue, right upper quadrant abdominal pain, elevated liver function tests, and jaundice (Culver et al., 2016).
- 7. Budd-Chiari syndrome: hepatic venous outflow obstruction (Mehta, 2019)
  - a) Incidence: 17% of cases (Khan et al., 2019)
  - b) Pathophysiology
    - (1) Drug-induced thrombosis of hepatic veins or inferior vena cava
    - (2) Centrizonal congestion, hepatocellular necrosis, hemorrhage
    - (3) Large regenerative nodules and obstructive portal venopathy
    - (4) Budd-Chiari syndrome includes classical (obstruction occurs within the hepatic vein and is more common in women), hepatic vena cava (inferior vena cava obstruction with or without the involvement of the hepatic veins and small vessel and more common in men), and small vessel versions (very rare; hepatic outflow obstruction limited to small intrahepatic veins) (Khan et al., 2019).
  - c) Signs and symptoms include painful hepatomegaly, jaundice, ascites, fever, pedal edema, dilated truncal veins, esophageal bleeding (less common), and hepatic encephalopathy (less common) (Khan et al., 2019).
- 8. Hepatic sinusoidal obstruction syndrome (SOS; formerly known as veno-occlusive disease): syndrome comprising weight gain, ascites, painful hepatomegaly, and jaundice caused by damage to the sinusoidal endothelial cells and leading to obstruction of the hepatic vessels (Botti et al., 2016; Corbacioglu et al., 2019; Gasmi & Kleiner, 2020; Mehta, 2019; Mohty et al., 2016; Nasserredine et al., 2018; Shehu et al., 2017; Tewari et al., 2017; Valla & Cazals-Hatem, 2016)
  - a) Incidence: approximately 14% of patients following allogeneic hematopoietic stem cell transplantation (HSCT) (range 0%–62%, depending on the series) (Corbacioglu et al., 2020)
    - (1) SOS is a complication of HSCT that most often occurs 20–30 days after receiving the conditioning regimen (Valla & Cazals-Hatem, 2016).
    - (2) The incidence of SOS following allogeneic HSCT has diminished, and outcomes have improved over the past decade (Nasserredine et al., 2018).
  - b) Pathophysiology
    - (1) Injury occurs to the sinusoids, hepatic veins, and hepatic arteries.
    - (2) Luminal narrowing of sinusoids leads to increased resistance to blood flow, resulting in hepatic congestion, sinusoidal dilation, and portal hypertension culminating in fibrosis.
    - (3) Thrombi may be seen in larger veins (Gasmi & Kleiner, 2020).
  - c) Risk factors (Corbacioglu et al., 2019)
    - (1) Patient-related factors
      - (a) Age
      - (b) Preexisting liver disease
      - (c) Underlying diagnosis (leukemia), advanced disease status
      - (d) Previous treatment (e.g., gemtuzumab ozogamicin, inotuzumab ozogamicin)
      - (e) Other previous organ toxicities (e.g., pulmonary, abdomen)
      - (f) Poor performance status
      - (g) Genetic factors
      - (h) Elevated ferritin
    - (2) Transplantation-related factors
      - (a) Allogeneic donor
      - (b) Previous transplant
      - (c) Myeloablative conditioning
      - (d) Graft-versus-host disease prophylaxis
      - (e) Antithymocyte globulin (horse)
  - d) Signs and symptoms include painful hepatomegaly, ascites, abdominal pain, weight gain, and hyperbilirubinemia (Corbacioglu et al., 2020; Hoofnagle & Björnsson, 2019; Tewari et al., 2017).
  - e) Assessment: Two grading systems have historically been used to diagnose and stage SOS—the Baltimore criteria (Bonifazi et al., 2020) and the modified Seattle criteria (Cairo et al., 2020; Corbacioglu et al., 2019).

- (1) The Baltimore criteria are more stringent, with an absolute requirement for hyperbilirubinemia. The severity of SOS can be classified retrospectively using the Seattle criteria (Nassereddine et al., 2018).
    - (2) The European Group for Blood and Marrow Transplantation (formerly the European Society for Blood and Marrow Transplantation) has proposed revised criteria for diagnosis and grading in adults and children (Corbacioglu et al., 2019; Faraci et al., 2019; Mohty et al., 2016; see Table 18-2).
  9. Neoplastic lesions: Focal nodular hyperplasia and hepatocellular adenomas have been seen with hepatotoxic drugs (Mehta, 2019).
    - a) Incidence: 6% of cases (Mehta, 2019)
    - b) Pathophysiology: focal nodular hyperplasia, hepatocellular adenomas
    - c) Signs and symptoms include abdominal distension, jaundice, weight loss, easy bruising, and right upper quadrant pain.
  10. Immune-related adverse events (Ellithi et al., 2020; Gordon et al., 2017)
    - a) Incidence: 2%–10% cases (Park et al., 2021)
      - (1) May occur with checkpoint inhibitors (e.g., cytotoxic T-lymphocyte antigen 4–blocking antibodies, programmed cell death protein 1 inhibitors, programmed cell death-ligand 1 inhibitors), chimeric antigen receptor T-cell therapies, monoclonal antibodies (Sosa et al., 2018; Spain et al., 2016; Winer et al., 2018)
      - (2) May present 6–14 weeks after initiation of therapy (Durrechou et al., 2020)
    - b) Pathophysiology
      - (1) Inflammation of hepatocytes or bile ducts
      - (2) Diffuse T-cell infiltrates of the liver
      - (3) Portal fibrosis (Nishida & Kudo, 2019)
    - c) Signs and symptoms include asymptomatic elevations in liver enzymes (at least three times the upper limit of normal of aspartate aminotransferase and alanine aminotransferase or twice the total bilirubin), hepatomegaly, and enlarged perihepatic lymph nodes.
- G. Assessment (Bhandari et al., 2018; Botti et al., 2016; Chalasani et al., 2021; Haanen et al., 2017; Helissey et al., 2016; Herrine, 2016; Kwo et al., 2017; Meunier & Larrey, 2019; Newsome et al., 2018; Skood, 2019; Sosa et al., 2018; Spain et al., 2016; Winer et al., 2018)
1. Medical history
    - a) Previous medications (e.g., prescription, illicit or recreational, herbal, dietary supplements) (Miller et al., 2020)
    - b) Alcohol use
    - c) Hepatitis
    - d) Familial history of liver disease
    - e) Risk factor exposure for viral hepatitis (e.g., IV drug use, transfusions, travel, sexual contacts, occupation, body piercings, tattoos)
    - f) Exposure to hepatic toxins
    - g) Organ transplants
    - h) Previous complications (e.g., bleeding, infection, renal failure)
    - i) Other conditions (e.g., congestive hepatopathy, diabetes, skin pigmentation, arthritis, hypogonadism and dilated cardiomyopathy, obesity, primary sclerosing cholangitis, early-onset emphysema, celiac disease, thyroid disease)
  2. Vital signs (e.g., fever, hypotension, hypertension, bradycardia, tachycardia)
  3. Laboratory testing should be obtained prior to each treatment and every 6–12 weeks for the first six months following completion of cancer therapies. Depending on treatment response or occurrence of toxicities, increased frequency of follow-up testing may be necessary.
    - a) Complete blood counts (including eosinophil count) (Chalasani et al., 2021)
    - b) Thyroid function tests
    - c) Liver function tests (e.g., bilirubin, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, alkaline phosphatase)
    - d) Complete metabolic panels
    - e) Coagulation factors
    - f) Hepatitis titers and viral hepatitis serologies (e.g., anti-hepatitis A immunoglobulin M antibody, surface antigen of the hepatitis B virus [HBsAg], anti-hepatitis B core antigen immunoglobulin M, anti-hepatitis C, hepatitis B RNA) (Chalasani et al., 2021)
  4. Physical examination should include a thorough head-to-toe assessment to identify signs and symptoms of hepatotoxicity.
    - a) Neurologic examination: Assess level of consciousness, orientation, and behavioral changes.
    - b) Examination of skin and head, eyes, ears, nose, and throat: Assess for jaundice of the skin, sclerae (icteric), and mucous membranes; rash; ecchymosis; and petechiae.
    - c) Cardiac and pulmonary examination: Assess for hypotension or hypertension, bradycardia or tachycardia, jugular venous distension, peripheral edema, crackles and rales, and weight gain.
    - d) Abdominal examination: Assess for bowel sounds, ascites, hepatosplenomegaly, abdominal pain, and hematemesis.

**TABLE 18-2.** Diagnosis and Grading of Sinusoidal Obstruction Syndrome

| System                                                                                                                                                                               | Diagnostic Criteria                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Grading and Severity                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Baltimore criteria<br>(Bonifazi et al., 2020)                                                                                                                                        | Serum bilirubin > 34 $\mu\text{mol/L}$ (> 2 mg/dl) within 21 days of transplantation and at least 2 of the following criteria: <ul style="list-style-type: none"> <li>• Hepatomegaly</li> <li>• &gt; 5% weight gain from baseline</li> <li>• Ascites</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | –                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| European Group for Blood and Marrow Transplantation diagnostic criteria for diagnosis of sinusoidal obstruction syndrome in adults<br>(Corbacioglu et al., 2019; Mohty et al., 2016) | In first 21 days after transplantation <ul style="list-style-type: none"> <li>• Bilirubin &gt; 34 <math>\mu\text{mol/L}</math> (&gt; 2 mg/dl) plus 2 of the following: <ul style="list-style-type: none"> <li>– Painful hepatomegaly</li> <li>– Weight gain &gt; 5% from baseline</li> <li>– Ascites</li> </ul> </li> </ul> Greater than 21 days after transplantation <ul style="list-style-type: none"> <li>• Classical sinusoidal obstruction syndrome, or</li> <li>• Histologically proved sinusoidal obstruction syndrome, or</li> <li>• 2 or more of the following: <ul style="list-style-type: none"> <li>– Painful hepatomegaly</li> <li>– Weight gain &gt; 5% from baseline</li> <li>– Ascites</li> <li>– Hemodynamic or ultrasound evidence of sinusoidal obstruction syndrome</li> </ul> </li> </ul> | –                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| European Group for Blood and Marrow Transplantation diagnostic criteria for diagnosis of sinusoidal obstruction syndrome in children<br>(Corbacioglu et al., 2018)                   | No time limitation for onset<br>Presence of 2 or more of the following criteria: <ul style="list-style-type: none"> <li>• Steroid-refractory thrombocytopenia (unexplained)</li> <li>• Unexplained weight gain for 3 consecutive days unresponsive to treatment or weight gain &gt; 5% above baseline</li> <li>• Hepatomegaly above baseline value (preferably confirmed with imaging)</li> <li>• Ascites above baseline value (preferably confirmed with imaging)</li> <li>• Elevated bilirubin above baseline for 3 consecutive days or <math>\geq 2</math> mg/dl within 72 hours</li> </ul>                                                                                                                                                                                                                  | –                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Modified Seattle criteria<br>(Cairo et al., 2020)                                                                                                                                    | At least 2 of the following, occurring within 20 days of transplantation: <ul style="list-style-type: none"> <li>• Serum bilirubin &gt; 34 <math>\mu\text{mol/L}</math> (&gt; 2 mg/dl)</li> <li>• Hepatomegaly with right upper quadrant pain</li> <li>• &gt; 2% weight gain from baseline due to fluid retention</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Mild <ul style="list-style-type: none"> <li>• No adverse effects of liver disease, and</li> <li>• No medications required for diuresis or hepatic pain, and</li> <li>• All symptoms, signs, and laboratory features reversible</li> </ul> Moderate <ul style="list-style-type: none"> <li>• Adverse effects of liver disease present, and</li> <li>• Sodium restriction or diuretics required, or</li> <li>• Medication for hepatic pain required, and</li> <li>• All symptoms, signs, and laboratory features reversible</li> </ul> Severe <ul style="list-style-type: none"> <li>• Adverse effects of liver disease present, and</li> <li>• Symptoms, signs, or laboratory features not resolved by day +100, or</li> <li>• Death</li> </ul> |

## H. Collaborative management (Lee & Chan, 2016; Vicenzi et al., 2016)

1. An interprofessional approach and collaboration among providers, nurses, patients, caregivers, and consultants are essential in managing patients who may develop hepatotoxicity. Liver abnormalities may increase, fluctuate, or possibly resolve without intervention (Economopoulou & Psyrri, 2016; Trinh et al., 2019).

a) Monitoring of liver function tests should be more frequent (every one to three days) until stabilization, followed by weekly monitoring (Trinh et al., 2019).

b) Nurses should rule out other causes, such as disease progression, infection, effects of other medications, hemochromatosis, or alcohol use (Sosa et al., 2018; Spain et al., 2016; Winer et al., 2018).

c) Standardized toxicity grading tools should be used.

(1) The National Cancer Institute Cancer Therapy Evaluation Program's (2017) *Common Terminology Criteria for Adverse Events* is a standardized classification to quantify or grade the severity of treatment-related adverse effects, including liver enzyme elevations (see Table 18-3).

(2) The Child-Pugh classification is a scoring system used to measure the severity of chronic liver disease, including cirrhosis, and provides clinicians a way to communicate objectively about liver function (Peng et al., 2016; see Table 18-4). The modified Child-Pugh score classifies liver disease severity according to the degree of ascites, serum concentrations of bilirubin and albumin, prothrombin time, and degree of encephalopathy.

d) Consider an autoimmunity workup, including serum antinuclear antibody, smooth muscle antibody, antimitochondrial antibodies, anti-soluble liver antigen/liver-pancreas antibodies, anti-liver-kidney microsomal type 1 antibodies, and additional studies as appropriate.

e) Consider viral screening, including Epstein-Barr virus, cytomegalovirus, hepatitis B and C, and hepatitis A, D, and E if the patient has a recent history of travel outside of the country (DeSouza & Savva, 2016).

f) Additional laboratory tests include complete metabolic panel, complete blood counts, ammonia level, coagulation factors, novel biomarkers (microRNA-122, cytokeratin 18, glutamate dehydrogenase, macrophage-colony-stimulating factor receptor 1, bile acids), and pharmacogenetic

markers (Chalasani et al., 2021; Meunier & Larrey, 2019).

g) Consider consultation with a gastroenterologist or hepatologist.

h) Consider imaging (DeSouza & Savva, 2016; Gordon et al., 2017).

(1) Ultrasound of the liver with or without Doppler can rule out obstruction of the biliary tree and assess for masses in the liver parenchyma (Chalasani et al., 2021).

(2) A computed tomography scan may identify hepatomegaly, periportal edema, or periportal lymphadenopathy. Other findings that may be noted include liver abnormalities, such as fatty liver, pseudo-cirrhosis, biliary sclerosis, and SOS (Torri et al., 2021).

(3) Magnetic resonance imaging with or without magnetic resonance cholangiopancreatography can evaluate the liver, gallbladder, bile ducts, pancreas, and pancreatic duct for disease (Chalasani et al., 2021).

i) A liver biopsy may be considered if the diagnosis remains unclear (DeSouza & Savva, 2016; Postow, 2015).

(1) Autoimmune hepatitis and drug-induced liver injury may present similarly, and a liver biopsy would provide a definitive diagnosis of the causative agent (Zen & Yeh, 2019). Severe inflammation of the lobules in the liver with thickening of the surrounding hepatic veins has been seen, leading to necrosis.

(2) Primary biliary pattern with mild portal mononuclear infiltration around proliferated bile ductules has been seen.

(a) Consider dose adjustment of drugs if hepatic dysfunction is noted at baseline (Wilkes & Barton-Burke, 2020).

(b) Consider avoiding hepatotoxic drugs in patients with preexisting liver dysfunction (Shehu et al., 2017).

(c) Consider withdrawal of the offending hepatotoxic drug and monitoring for normalization of liver function tests.

## 2. Management of immune-mediated hepatitis

a) The primary mode of treatment for hepatotoxicity is the withdrawal of the offending drug. Management algorithms have been developed based on the severity of the toxicity (Darnell et al., 2020; Ellithi et al., 2020; Fay et al., 2016; Jennings et al., 2019; Kwo et al., 2017; Mistry et al., 2017; Morgado et al., 2020; Naidoo et al., 2015; Newsome et al., 2018; Park et al., 2021; Sosa et al.,



**TABLE 18-3.** Common Terminology Criteria for Adverse Events Grading for Liver Toxicity<sup>a</sup>

| Adverse Event                           | Grade                                                                                  |                                                                                      |                                                                                                          |                                                                                |       |
|-----------------------------------------|----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|-------|
|                                         | 1                                                                                      | 2                                                                                    | 3                                                                                                        | 4                                                                              | 5     |
| Alanine aminotransferase increased      | > ULN–3 × ULN if baseline was normal;<br>1.5–3 × baseline if baseline was abnormal     | > 3–5 × ULN if baseline was normal;<br>> 3–5 × baseline if baseline was abnormal     | > 5–20 × ULN if baseline was normal;<br>> 5–20 × baseline if baseline was abnormal                       | > 20 × ULN if baseline was normal;<br>> 20 × baseline if baseline was abnormal | –     |
| Alkaline phosphatase increased          | > ULN–2.5 × ULN if baseline was normal;<br>2–2.5 × baseline if baseline was abnormal   | > 2.5–5 × ULN if baseline was normal;<br>> 2.5–5 × baseline if baseline was abnormal | > 5–20 × ULN if baseline was normal;<br>> 5–20 × baseline if baseline was abnormal                       | > 20 × ULN if baseline was normal;<br>> 20 × baseline if baseline was abnormal | –     |
| Aspartate aminotransferase increased    | > ULN–3 × ULN if baseline was normal;<br>1.5–3 × baseline if baseline was abnormal     | > 3–5 × ULN if baseline was normal;<br>> 3–5 × baseline if baseline was abnormal     | > 5–20 × ULN if baseline was normal;<br>> 5–20 × baseline if baseline was abnormal                       | > 20 × ULN if baseline was normal;<br>> 20 × baseline if baseline was abnormal | –     |
| Gamma-glutamyl transpeptidase increased | > ULN–2.5 × ULN if baseline was normal;<br>2–2.5 × baseline if baseline was abnormal   | > 2.5–5 × ULN if baseline was normal;<br>2.5–5 × baseline if baseline was abnormal   | > 5–20 × ULN if baseline was normal;<br>> 5–20 × baseline if baseline was abnormal                       | > 20 × ULN if baseline was normal;<br>> 20 × baseline if baseline was abnormal | –     |
| Liver failure (clinical)                | –                                                                                      | –                                                                                    | Asterixis; mild encephalopathy; drug-induced liver injury; limiting self-care activities of daily living | Life-threatening consequences; moderate to severe encephalopathy; coma         | Death |
| Portal hypertension                     | –                                                                                      | Decreased portal vein flow                                                           | Reversal/retrograde portal vein flow; associated with varices and/or ascites                             | Life-threatening consequences; urgent intervention indicated                   | Death |
| Total bilirubin increased               | > ULN–1.5 × ULN if baseline was normal;<br>> 1–1.5 × baseline if baseline was abnormal | > 1.5–3 × ULN if baseline was normal;<br>> 1.5–3 × baseline if baseline was abnormal | > 3–10 × ULN if baseline was normal;<br>> 3–10 × baseline if baseline was abnormal                       | > 10 × ULN if baseline was normal;<br>> 10 × baseline if baseline was abnormal | –     |

<sup>a</sup>Grading criteria for additional hepatobiliary disorders are available in the *Common Terminology Criteria for Adverse Events*.

ULN—upper limit of normal

Note. From *Common Terminology Criteria for Adverse Events* [v5.0], by National Cancer Institute Cancer Therapy Evaluation Program, 2017 ([https://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/docs/CTCAE\\_v5\\_Quick\\_Reference\\_5x7.pdf](https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf)). In the public domain.

- 2018; Spain et al., 2016; Thompson et al., 2019; Villadolid & Amin, 2015; Winer et al., 2018).
- b) Mild (grade 1) immune-related adverse events warrant close monitoring of liver enzymes and supportive care (Ellithi et al., 2020).
- c) Moderate or severe (grade 2) immune-related adverse events necessitate holding the drug and initiating corticosteroids (Economopoulou & Psyrris, 2016).
- d) The drug is resumed when toxicity is grade 1 or less.
- e) Severe or life-threatening (grade 3–4) immune-related adverse events require permanent discontinuation of the drug and initiation of high-dose corticosteroids.
- f) Steroids are tapered gradually over at least one month.
- g) In the presence of steroid-refractory hepatitis, mycophenolate or antithymocyte globulin, tacrolimus, and azathioprine should be considered (Choi & Lee, 2020; DeSouza & Savva, 2016; Economopoulou & Psyrris, 2016; Eigentler et al., 2016; Lampson et al., 2016; Sanjeevaiah et al., 2018).
- I. Patient and family education (Chalasani et al., 2021; Champiat et al., 2016; Economopoulou & Psyrris, 2016)
  - 1. Patient and caregiver education about the potential side effects of drugs is essential. Communication is critical, including an emphasis on the importance of



**TABLE 18-4.** Child-Pugh Classification of Severity of Cirrhosis

| Clinical and Laboratory Criteria                                                         | Points Assigned           |                                            |                                  |
|------------------------------------------------------------------------------------------|---------------------------|--------------------------------------------|----------------------------------|
|                                                                                          | 1                         | 2                                          | 3                                |
| Albumin                                                                                  | > 3.5 g/dl (35 g/L)       | 2.8–3.5 g/dl (28–35 g/L)                   | < 2.8 g/dl (< 28 g/L)            |
| Ascites                                                                                  | None                      | Mild to moderate (responsive to diuretics) | Severe (refractory to diuretics) |
| Bilirubin                                                                                | < 2 mg/dl (< 34.2 μmol/L) | 2–3 mg/dl (34.2–51.3 μmol/L)               | > 3 mg/dl (> 51.3 μmol/L)        |
| Encephalopathy                                                                           | Grade 0 (none)            | Grade 1–2                                  | Grade 3–4                        |
| Prothrombin time (PT; in seconds over normal value)/international normalized ratio (INR) | PT < 4; INR < 1.7         | PT 4–6; INR 1.7–2.3                        | PT > 6; INR > 2.3                |
| Total Score                                                                              | Grade                     | Description                                | 1- and 2-Year Survival           |
| 5–6                                                                                      | A                         | Well-compensated disease                   | 100%; 85%                        |
| 7–9                                                                                      | B                         | Significant functional compromise          | 80%; 60%                         |
| 10–15                                                                                    | C                         | Decompensated disease                      | 45%; 35%                         |

Note. Based on information from Durand & Valla, 2005; Pugh et al., 1973.

prompt identification and reporting of the following signs and symptoms:

- Change in level of consciousness (e.g., increased sedation, confusion)
  - Malaise, fever
  - Jaundice, icteric sclera
  - Abdominal pain, bleeding or persistent bruising, hematemesis, changes in stool or urine (including the presence of blood)
  - Edema of extremities, weight gain
- Items to include in patient instructions
    - Avoidance of other hepatotoxins, including herbal and dietary supplements and over-the-counter medications
    - Close follow-up with healthcare providers, including periodic monitoring of liver function studies
    - Maintenance of a well-balanced diet and hydration
    - Skin care (e.g., avoidance of scratching, use of lotions, daily showers)
    - Fall prevention

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## CHAPTER 19

# Genitourinary Toxicities

### A. Overview

1. The kidneys have multiple roles within the human body, with their primary functions including blood filtration, metabolism, excretion of endogenous and exogenous compounds, and endocrine functions (Perlman & Heung, 2019).

- a) Anatomically, the kidney comprises roughly one million nephrons, each of which includes a glomerulus (the site of blood filtration) and a renal tubule, where water and salts are reclaimed (Perlman & Heung, 2019).

- b) Many anticancer treatments, including specific chemotherapy and immunotherapy agents, are considered nephrotoxic because they are metabolized via the renal system. Therefore, many therapies necessitate careful monitoring and possible dose modifications to prevent kidney injury, which can be irreversible in some cases (Shahinian et al., 2017).

2. The bladder consists of three layers: the mucosa, submucosa, and muscularis. Chemotherapy drugs can result in the recruitment of inflammatory mediators, including myeloperoxidase, interleukin-1-beta, and interleukin-6, which result in edema, hemorrhage, and vascular permeability in the bladder layers (Dornelas-Filho et al., 2018). Radiation therapy can induce a hypoxic injury, resulting in endarteritis in small vessels and fibrotic changes to the mucosa and submucosa layers (Tanaka et al., 2019).

### B. Antineoplastic-associated genitourinary toxicities

#### 1. Acute kidney injury (AKI)

##### a) Definition and pathophysiology

- (1) AKI is a sudden loss of kidney function over hours to days, resulting in fluid and electrolyte imbalances, acid-base irregularity, and retention of nitrogenous waste products in the blood (Mercado et al., 2019).

- (2) A universal definition and staging system were developed by the collaborative efforts

of KDIGO (Kidney Disease: Improving Global Outcomes), RIFLE (Risk, Injury, Failure, Loss, End-stage renal disease), and the Acute Kidney Injury Network.

- (3) AKI includes an increase in serum creatinine by greater than or equal to 0.3 mg/dl within 48 hours or an increase in serum creatinine by greater than or equal to 1.5 times baseline, which is known or presumed to have occurred within the prior seven days, or urine volume less than 0.5 ml/kg/hour for six hours.

- (4) AKI staging increases with an escalating insult to creatinine and a reduction in urine output (International Society of Nephrology, 2012; Mercado et al., 2019; see Figure 19-1).

- b) AKI etiology is multifactorial and includes prerenal, intrinsic, or postrenal causes.

- (1) Prerenal causes occur with decreased perfusion and subsequent glomerular filtration rate (GFR).

- (a) Etiology includes any insult that would cause intravascular volume depletion, such as hypovolemia, peripheral vasodilation, decreased arterial pressures, or impaired cardiac function.

- (b) Infections, such as sepsis and drugs lowering renal perfusion, are also associated with prerenal etiology.

- (2) Intrinsic causes include injury to the glomerulus, tubule, tubular interstitial, and kidney microvasculature. A disease affecting the vasculature of the kidney, such as renal artery thrombosis, will also result in intrinsic injury.

- (3) Postrenal causes include any injury induced by obstruction of urinary flow, such as prostatic hypertrophy or extra-renal compression from a bladder

**FIGURE 19-1.** Definition of Acute Kidney Injury**Section 2: AKI Definition**

2.1.1: AKI is defined as any of the following (Not Graded):

- Increase in SCr by  $\geq 0.3$  mg/dl ( $\geq 26.5$   $\mu\text{mol/L}$ ) within 48 hours; or
- Increase in SCr to  $\geq 1.5$  times baseline, which is known or presumed to have occurred within the prior 7 days; or
- Urine volume  $< 0.5$  ml/kg/h for 6 hours.

2.1.2: AKI is staged for severity according to the following criteria (Table 2). (Not Graded)

**Table 2 | Staging of AKI**

| Stage | Serum creatinine                                                                                                                                                                                                                                          | Urine output                                                            |
|-------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|
| 1     | 1.5–1.9 times baseline<br>OR<br>$\geq 0.3$ mg/dl ( $\geq 26.5$ $\mu\text{mol/L}$ ) increase                                                                                                                                                               | $< 0.5$ ml/kg/h for 6–12 hours                                          |
| 2     | 2.0–2.9 times baseline                                                                                                                                                                                                                                    | $< 0.5$ ml/kg/h for $\geq 12$ hours                                     |
| 3     | 3.0 times baseline<br>OR<br>Increase in serum creatinine to $\geq 4.0$ mg/dl ( $\geq 353.6$ $\mu\text{mol/L}$ )<br>OR<br>Initiation of renal replacement therapy<br>OR, In patients $< 18$ years, decrease in eGFR to $< 35$ ml/min per $1.73\text{ m}^2$ | $< 0.3$ ml/kg/h for $\geq 24$ hours<br>OR<br>Anuria for $\geq 12$ hours |

AKI—acute kidney injury; eGFR—estimated glomerular filtration rate

Note. From "KDIGO Clinical Practice Guideline for Acute Kidney Injury," by Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2012, *Kidney International Supplements*, 2(1), p. 8 (<https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-AKI-Guideline-English.pdf>). Copyright 2012 by KDIGO. Reprinted with permission.

or retroperitoneal tumor (Mercado et al., 2019).

- (4) Increases in mortality, length of hospital stay, and chemotherapy dose reductions are associated with AKI in patients with cancer, making prevention and effective monitoring crucial to oncology nursing practice.
- (5) Due to the varying definitions of AKI and changes in treatment patterns, the exact incidence is unknown; however, recent studies suggest incidence is 11%–20%, with a higher risk associated with hematologic malignancy (Rosner et al., 2017).
- (6) Overall, renal cell cancer, liver cancer, multiple myeloma, leukemia, and hematopoietic stem cell transplantation (HSCT) are associated with the highest incidences (Rosner et al., 2017; see Table 19-1).

c) Risk factors

(1) Pharmacologic agents

(a) Chemotherapy

- i. Conventional chemotherapies result in direct cellular toxicity, oxidative stress, mitochondrial injury, and apoptosis.

ii. Acute tubular injury can be seen with platinum agents, ifosfamide, and pemetrexed.

iii. Interstitial nephritis can also be associated with conventional agents, such as doxorubicin (Rosner et al., 2017).

(b) Targeted therapies

i. Targeted agents may be associated with AKI, proteinuria, hypertension, and electrolyte disturbances.

ii. Thrombotic microangiopathy may occur with antiangiogenesis drugs targeting vascular endothelial growth factors.

iii. BRAF inhibitors, such as vemurafenib and dabrafenib, are associated with dose-related AKI that can often resolve with drug discontinuation.

iv. Tubulointerstitial injury is only partially reversible with crizotinib (Rosner et al., 2017).



**TABLE 19-1.** Genitourinary Toxicities

| Classification             | Drug                                | Side Effects and Toxicities                                         | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|----------------------------|-------------------------------------|---------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Chemotherapy Agents</b> |                                     |                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Alkylating agents          | Bendamustine (Bendeka®)             | Increased serum creatinine                                          | The drug is associated with TLS when given in patients with increased tumor burden.<br>Use with caution in patients with mild to moderate renal impairment.<br>The drug is not recommended in patients with CrCl < 30 ml/min. (Teva Pharmaceuticals, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|                            | Carboplatin                         | AKI                                                                 | The drug exhibits less renal toxicity than cisplatin.<br>Check creatinine level before each dose (for area under the curve dosing). Refer to Chapter 11. (Teva Pharmaceuticals, 2016a)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                            | Cisplatin (Platinol®, Platinol®-AQ) | Severe dose-related and cumulative renal toxicity, including AKI    | Monitor creatinine, blood urea nitrogen, CrCl, and electrolytes. Ensure adequate hydration prior to, during, and postadministration.<br>Monitor urinary output and ensure magnesium repletion as needed.<br>Renal toxicity typically presents the second week after administration.<br>Older adult patients and those with preexisting renal impairment are more susceptible to renal toxicity.<br>Dose reductions are needed in the setting of baseline renal impairment or following significant CrCl reductions during treatment.<br>Consideration of alternative therapies is also appropriate.<br>Dose reductions for curative intent therapy should begin with GFR 50–59 ml/min/1.73m <sup>2</sup> .<br>Therapy is not recommended at GFR < 40 ml/min/1.73 m <sup>2</sup> .<br>For palliative intent, dose reductions begin at GFR 50–59 ml/min/1.73 m <sup>2</sup> .<br>In this setting, therapy is not recommended at GFR < 50 ml/min/1.73 m <sup>2</sup> .<br>(Krens et al., 2019; WG Critical Care, 2019) |
|                            | Cyclophosphamide (Cytoxan®)         | Renal toxicity, hemorrhagic cystitis, SIADH, dose-related sterility | Dose adjust for CrCl beginning at ≤ 29 ml/min. See drug-specific criteria.<br>Dose reductions are required for hemodialysis and peritoneal dialysis. No dose reduction is required for continuous renal replacement therapy.<br>Increase fluid intake 1–2 days after the dose to avoid bladder toxicity (hemorrhagic cystitis).<br>In hematopoietic stem cell transplantation, mesna and hyperhydration with or without forced diuresis are recommended for high-dose cyclophosphamide.<br>(Baxter Healthcare, 2017; Hensley et al., 2009; Krens et al., 2019)                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|                            | Ifosfamide (Ifex®)                  | Hemorrhagic cystitis                                                | The drug may cause severe nephrotoxicity, resulting in renal failure.<br>The drug is associated with proteinuria and SIADH.<br>Mesna should be used to reduce the incidence of hemorrhagic cystitis.<br>(Baxter Healthcare, 2018)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                            | Melphalan (Alkeran®, Evomela®)      | Hypokalemia, renal failure or insufficiency                         | The drug is associated with SIADH.<br>Dose reductions should be considered in patients receiving palliative treatment with renal insufficiency.<br>(Spectrum Pharmaceuticals, 2016)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

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**TABLE 19-1. Genitourinary Toxicities (Continued)**

| Classification                     | Drug                            | Side Effects and Toxicities                                                           | Nursing Considerations                                                                                                                                                                                                                                                                                                                |
|------------------------------------|---------------------------------|---------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Chemotherapy Agents (Cont.)</b> |                                 |                                                                                       |                                                                                                                                                                                                                                                                                                                                       |
| Alkylating agents (Cont.)          | Oxaliplatin (Eloxatin®)         | Acute tubular necrosis, acute interstitial nephritis, AKI, increased serum creatinine | The drug is associated with hypokalemia and dehydration. Dose adjust for CrCl < 30 ml/min. (Sanofi-Aventis U.S., 2020b)                                                                                                                                                                                                               |
| Antimetabolites                    | Azacitidine (Vidaza®)           | Renal failure                                                                         | Monitor serum creatinine. The drug is primarily excreted by the kidneys. The drug is associated with TLS in patients with high tumor burden. Dose reductions may be necessary for patients with serum creatinine or blood urea nitrogen elevations. (Celgene, 2020)                                                                   |
|                                    | Capecitabine (Xeloda®)          | Dehydration, renal insufficiency                                                      | Monitor for and correct dehydration. Dose reductions are indicated in patients with moderate renal impairment. The drug is contraindicated in patients with CrCl < 30 ml/min. The drug is associated with the risk of dehydration resulting in AKI. Exercise caution with concomitant use with nephrotoxic agents. (Genentech, 2021c) |
|                                    | Clofarabine (Clolar®)           | AKI                                                                                   | Monitor renal function during the days of administration. Dose reduction is necessary for patients with renal impairment (< 60 ml/min). (Sanofi-Aventis U.S., 2016)                                                                                                                                                                   |
|                                    | Fludarabine                     | Renal failure or insufficiency                                                        | Monitor CrCl. Dose adjust for patients with moderate impairment of renal function. (Teva Pharmaceuticals, 2017)                                                                                                                                                                                                                       |
|                                    | Gemcitabine (Gemzar®)           | Renal failure or insufficiency, proteinuria, hemolytic uremic syndrome                | Monitor serum creatinine and blood urea nitrogen. Permanently discontinue for hemolytic uremic syndrome or severe renal impairment. (Eli Lilly and Company, 2019b)                                                                                                                                                                    |
|                                    | Hydroxyurea (Hydrea®, Mylocel®) | Renal failure                                                                         | Reduce the dose of hydroxyurea in patients with creatinine clearance < 60 ml/min. (Bristol-Myers Squibb, 2017)                                                                                                                                                                                                                        |
|                                    | Methotrexate                    | AKI (dose dependent)                                                                  | The drug can cause crystal nephropathy when given at high doses. Maintain adequate hydration and urinary alkalization. Renal excretion is the primary route of elimination, and impaired renal function increases the risk of methotrexate toxicity. (Fresenius Kabi, 2020)                                                           |
|                                    | Nelarabine (Arranon®)           | Renal impairment                                                                      | Closely monitor patients with moderate or severe renal impairment for toxicities. (Novartis Pharmaceuticals, 2019)                                                                                                                                                                                                                    |
|                                    | Pemetrexed (Alimta®)            | Renal failure                                                                         | The drug is not recommended in patients with CrCl < 45 ml/min. Ibuprofen drug interaction can cause increased toxicity in patients with mild or moderate renal impairment. Avoid ibuprofen for 2 days prior to, the day of, and 2 days following administration of pemetrexed. (Eli Lilly and Company, 2019a)                         |

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**TABLE 19-1.** Genitourinary Toxicities (*Continued*)

| Classification                     | Drug                                  | Side Effects and Toxicities                                                               | Nursing Considerations                                                                                                                                                                                                                                                                                                                                            |
|------------------------------------|---------------------------------------|-------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Chemotherapy Agents (Cont.)</b> |                                       |                                                                                           |                                                                                                                                                                                                                                                                                                                                                                   |
| Antimetabolites<br>(Cont.)         | Pentostatin<br>(Nipent™)              | Renal failure or insufficiency                                                            | Severe renal toxicities can result in higher-than-recommended doses.<br>Discontinue drug if CrCl < 30 ml/min.<br>(Hospira, 2019)                                                                                                                                                                                                                                  |
|                                    | Pralatrexate<br>(Folotyng)            | Renal insufficiency                                                                       | Concomitant administration of drugs that are subject to substantial renal clearance (e.g., nonsteroidal anti-inflammatory drugs, trimethoprim-sulfamethoxazole) may result in delayed clearance of pralatrexate.<br>(Acrotech Biopharma, 2020b)                                                                                                                   |
| Antitumor antibiotics              | Bleomycin<br>(Blenoxane®)             | Renal insufficiency                                                                       | Dose adjust for CrCl < 50 ml/min.<br>Renal insufficiency alters drug elimination, as it is primarily excreted by the kidneys.<br>(Fresenius Kabi, 2016)                                                                                                                                                                                                           |
|                                    | Mitomycin C<br>(Mitosol®, Mutamycin®) | Renal failure or insufficiency                                                            | Do not administer if serum creatinine > 1.7 mg/dl<br>The drug is associated with hemolytic-uremic syndrome.<br>(Accord BioPharma, 2016)                                                                                                                                                                                                                           |
| Miscellaneous                      | Arsenic trioxide<br>(Trisenox®)       |                                                                                           | Use with caution in patients with renal impairment.<br>Monitor electrolytes during therapy. Maintain serum potassium > 4 mEq/L and magnesium > 1.8 mg/dl.<br>Renal impairment may increase toxicity risk.<br>(Teva Pharmaceuticals, 2016b)                                                                                                                        |
| <b>Targeted Therapy Agents</b>     |                                       |                                                                                           |                                                                                                                                                                                                                                                                                                                                                                   |
| Small molecule inhibitors          | Afinib<br>(Gilotrif®)                 | Cystitis, decreased CrCl                                                                  | Monitor creatinine, hydration status, and for signs of cystitis.<br>(Boehringer Ingelheim, 2019)                                                                                                                                                                                                                                                                  |
|                                    | Alectinib<br>(Alecensa®)              | Renal toxicity, AKI, electrolyte abnormalities                                            | The median time to grade ≥ 3 renal impairment is 3.7 months (range 0.5–14.7 months).<br>Grade 3 renal impairment: Hold until baseline creatinine or equal to 1.5 × ULN, then resume at a reduced dose.<br>Discontinue drug at grade 4.<br>See package insert for dose reduction instructions.<br>Monitor serum electrolytes and creatinine.<br>(Genentech, 2021a) |
|                                    | Belinostat<br>(Beleodaq®)             | Tumor lysis syndrome with advanced-stage disease or significant tumor burden, hypokalemia | Monitor electrolytes, creatinine, and CrCl.<br>Follow package insert guidelines for dose modification.<br>Insufficient evidence exists to recommend therapy if CrCl ≤ 39 ml/min.<br>(Acrotech Biopharma, 2020a)                                                                                                                                                   |
|                                    | Bosutinib<br>(Bosulif®)               | Acute kidney injury, renal failure or insufficiency                                       | A declined GFR has been observed.<br>Monitor serum creatinine.<br>Dose reduce for renal impairment.<br>(Pfizer, 2021)                                                                                                                                                                                                                                             |
|                                    | Brigatinib<br>(Alunbrig®)             | Hypertension, electrolyte abnormalities, hyperglycemia                                    | Drugs should be initially held and medical intervention initiated at grade 3 hypertension.<br>Resume at lower doses at grade 1 toxicity according to the package insert.<br>The drug should be held at grade 4 hypertension and may result in drug discontinuation.<br>Monitor electrolytes, creatinine, and glucose.<br>(Takeda Pharmaceuticals, 2020)           |

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**TABLE 19-1.** Genitourinary Toxicities (*Continued*)

| Classification                                | Drug                         | Side Effects and Toxicities                                                                       | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-----------------------------------------------|------------------------------|---------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Targeted Therapy Agents (Cont.)</b>        |                              |                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Small molecule inhibitors<br>( <i>Cont.</i> ) | Carfilzomib (Kyprolis®)      | AKI                                                                                               | Nephrotoxicity has been reported and may cause fatal events. Monitor serum creatinine regularly. Renal failure is greater when patients have a baseline reduced CrCl. (Amgen, 2021)                                                                                                                                                                                                                                                     |
|                                               | Crizotinib (Xalkori®)        | Electrolyte abnormalities, renal cysts, AKI, GFR reductions beginning 2 weeks into therapy        | Monitor electrolytes, serum creatinine, and GFR. Dose reductions are recommended with severe renal impairment (CrCl < 30 ml/min). See package insert for further details. (Pfizer, 2021c)                                                                                                                                                                                                                                               |
|                                               | Dabrafenib (Tafinlar®)       | Hyponatremia, hypophosphatemia, hyperkalemia, increased creatinine, urinary tract infections, AKI | Monitor electrolytes and renal function. Dose reductions are not currently recommended for mild to moderate renal impairment; however, formalized pharmacokinetic studies are needed. Dose is not established for severe renal impairment. (Novartis Pharmaceuticals, 2021c)                                                                                                                                                            |
|                                               | Enasidenib (Idhifa®)         | Differentiation syndrome, which can be associated with renal insufficiency                        | Monitor for and treat differentiation syndrome if it occurs. (Celgene, 2021)                                                                                                                                                                                                                                                                                                                                                            |
|                                               | Erlotinib (Tarceva®)         | AKI, hepatorenal syndrome, renal insufficiency, urinary tract infection (< 4%)                    | Monitor serum creatinine and electrolytes. (Genentech, 2016)                                                                                                                                                                                                                                                                                                                                                                            |
|                                               | Everolimus (Afinitor®)       | AKI, proteinuria                                                                                  | Monitor drug levels as evidence shows trough levels > 26.3 ng/ml are associated with 4-fold increased risk of toxicity, and levels < 11.9 ng/ml are associated with a 3-fold increased risk of progression. Monitor renal function at baseline and at least every 6 months in those with risk factors. See package insert for guidelines on dose adjustments for toxicity. (Deppenweiler et al., 2017; Novartis Pharmaceuticals, 2021a) |
|                                               | Fedratinib (Inrebic®)        | Dysuria, urinary tract infections, renal insufficiency                                            | Monitor blood urea nitrogen, creatinine, and CrCl. Dose modifications are needed for severe renal impairment (CrCl 15–29 ml/min). See package insert for details. (Celgene, 2019a)                                                                                                                                                                                                                                                      |
|                                               | Gilteritinib (Xospata®)      | Renal insufficiency associated with differentiation syndrome                                      | Monitor for differentiation syndrome. Monitor serum creatinine. (Astellas Pharma, 2019)                                                                                                                                                                                                                                                                                                                                                 |
|                                               | Glasdegib (Daurismo®)        | AKI oliguria and renal failure, electrolyte abnormalities                                         | Monitor electrolytes, creatinine, and CrCl prior to, weekly for the first month, and monthly for the duration of therapy. (Pfizer, 2020a)                                                                                                                                                                                                                                                                                               |
|                                               | Imatinib mesylate (Gleevec®) | Increased serum creatinine, nephrotoxicity (including genitourinary)                              | The drug is associated with AKI and SIADH. Dose adjust for CrCl ≤ 39 ml/min. (Novartis Pharmaceuticals, 2020)                                                                                                                                                                                                                                                                                                                           |
|                                               | Infigratinib (Truseltiq®)    | Hyperphosphatemia, renal insufficiency                                                            | See package insert for specific instructions on dose adjustments for serum phosphorus starting at > 5.5 mg/dl. Dose reductions are needed for mild to moderate renal impairment (CrCl 30–89 ml/min). Dose is not established for severe or end-stage renal failure. (QED Therapeutics, 2021)                                                                                                                                            |

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**TABLE 19-1.** Genitourinary Toxicities (*Continued*)

| Classification                                | Drug                       | Side Effects and Toxicities                                                    | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-----------------------------------------------|----------------------------|--------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Targeted Therapy Agents (Cont.)</b>        |                            |                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Small molecule inhibitors<br>( <i>Cont.</i> ) | Ivosidenib<br>(Tibsovo®)   | Renal insufficiency associated with differentiation syndrome                   | Monitor serum creatinine during therapy.<br>Monitor for differentiation syndrome<br>For eGFR < 30 ml/min/1.73 m <sup>2</sup> and end-stage renal disease requiring dialysis, no dose adjustments are recommended per the manufacturer label (not studied); consider risks versus benefits for preexisting renal impairment.<br>(Servier Pharmaceuticals, 2021)                                                                                          |
|                                               | Ixazomib<br>(Ninlaro®)     | Tumor lysis syndrome, renal insufficiency                                      | Dose reductions are needed for severe renal impairment (CrCl < 30 ml/min) or end-stage renal disease requiring dialysis.<br>(Millennium Pharmaceuticals, 2021)                                                                                                                                                                                                                                                                                          |
|                                               | Lenvatinib<br>(Lenvima®)   | Hematuria, proteinuria, urinary tract infection, hypocalcemia                  | Monitor creatinine, electrolytes, and proteinuria baseline and periodically.<br>If 2+ protein on urine dipstick, withhold until ≤ 2 g/24 hours.<br>Permanently discontinue for nephrotic syndrome.<br>Renal impairment or failure can occur.<br>Major risk factors for renal impairment are dehydration or hypovolemia secondary to diarrhea and vomiting.<br>Dose adjustment is needed for specific cancers with CrCl < 15–29 ml/min.<br>(Eisai, 2021) |
|                                               | Lorlatinib<br>(Lorbrena®)  | Hypophosphatemia, hypomagnesia                                                 | Monitor serum electrolytes and renal function.<br>No dose adjustment is needed for mild or moderate renal impairment (CrCl 30–89 ml/min).<br>A recommended dose is not established in severe renal impairment.<br>(Pfizer, 2021b)                                                                                                                                                                                                                       |
|                                               | Pemigatinib<br>(Pemazyre®) | Hyperphosphatemia, urinary tract infections, dehydration, increased creatinine | Initiate a low phosphorus diet when serum phosphate > 5.5 mg/dl.<br>Start phosphate-lowering therapy and weekly labs for serum phosphate > 7 mg/dl.<br>See package insert for specifics on withholding and resuming.<br>Monitor renal function. Mean serum creatinine increase typically occurs by day 8 and subsequently decreases when off therapy.<br>(Incyte, 2021a)                                                                                |
|                                               | Ruxolitinib<br>(Jakafi®)   | Renal insufficiency, urinary tract infections, edema                           | Monitor renal function throughout therapy.<br>Dose reduction is required for moderate (CrCl 15–29 ml/min) to severe renal impairment (CrCl 15–29 ml/min).<br>See package insert for specific information.<br>Avoid therapy for end-stage renal disease (CrCl < 15 ml/min not requiring dialysis).<br>(Incyte, 2021b)                                                                                                                                    |
|                                               | Sunitinib<br>(Sutent®)     | Renal failure or insufficiency                                                 | Drug is associated with proteinuria, hypertension, and TLS.<br>Proteinuria occurs when urine protein ≥ 3 g per 24 hours. Interrupt drug and reduce the dose.<br>For persistent urine protein despite dose reductions, discontinue drug.<br>End-stage renal disease on hemodialysis may require subsequent dose reductions.<br>(Pfizer, 2020b)                                                                                                           |

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**TABLE 19-1.** Genitourinary Toxicities (*Continued*)

| Classification                                | Drug                                       | Side Effects and Toxicities                                                                 | Nursing Considerations                                                                                                                                                                                                                                                                                     |
|-----------------------------------------------|--------------------------------------------|---------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Targeted Therapy Agents (Cont.)</b>        |                                            |                                                                                             |                                                                                                                                                                                                                                                                                                            |
| Small molecule inhibitors<br>( <i>Cont.</i> ) | Talazoparib<br>(Talzenna™)                 | Anemia, thrombocytopenia                                                                    | Monitor renal function.<br>Dose reduction is required for moderate (CrCl 15–29 ml/min) to severe (CrCl 15–29 ml/min) renal impairment.<br>Dialysis has not been studied.<br>(Pfizer, 2020c)                                                                                                                |
|                                               | Temsirolimus<br>(Torisel®)                 | Increased serum creatinine, proteinuria (e.g., nephrotic syndrome), urinary tract infection | Monitor for renal function and urinary hesitancy, retention, oliguria, hematuria, and proteinuria baseline and periodically.<br>Discontinue drug in the setting of nephrotic syndrome.<br>(Pfizer, 2018)                                                                                                   |
|                                               | Trametinib<br>(Mekinist®)                  | Hyperglycemia, hemorrhage, rhabdomyolysis, hyponatremia, hypophosphatemia                   | Monitor electrolytes and renal function.<br>See package insert for dosage modifications for any adverse reaction ≥ grade 2.<br>(Novartis Pharmaceuticals, 2021b)                                                                                                                                           |
|                                               | Tucatinib<br>(Tukysa®)                     | AKI, hypokalemia, hyponatremia                                                              | Monitor renal function and serum electrolytes.<br>No dosage adjustment is recommended for mild to moderate renal impairment (CrCl 30–89 ml/min).<br>Do not use in combination with capecitabine and trastuzumab in severe renal failure (CrCl < 30 ml/min).<br>(Seattle Genetics, 2020)                    |
|                                               | Vandetanib<br>(Caprelsa®)                  | Hypertension/hypertensive crisis, renal insufficiency, hypomagnesemia, hypocalcemia         | Monitor renal function, serum electrolytes, and blood pressure.<br>Dose reduction is required for moderate (CrCl ≥ 30–50 ml/min) to severe (CrCl < 30 ml/min) renal impairment.<br>(Sanofi-Aventis U.S., 2020a)                                                                                            |
|                                               | Vemurafenib<br>(Zelboraf®)                 | Renal impairment                                                                            | Monitor serum creatinine at baseline and periodically during therapy.<br>Monitor electrolytes at baseline and with dose changes.<br>(Genentech, 2020)                                                                                                                                                      |
| <b>Immunotherapy Agents</b>                   |                                            |                                                                                             |                                                                                                                                                                                                                                                                                                            |
| Antibody-drug conjugate                       | Brentuximab vedotin<br>(Adcetris®)         | TLS (particularly with greater tumor burden)                                                | Monitor creatinine at baseline and throughout therapy.<br>Avoid use with CrCl < 30 ml/min.<br>Monomethylauristatin E, a component of brentuximab vedotin, is a microtubule disrupting agent.<br>Grade 3–4 renal impairment and death were increased in the setting of severe impairment.<br>(Seagen, 2020) |
| Cytokines: interleukins                       | Interleukin-2, aldesleukin<br>(Proleukin®) | AKI, hypomagnesemia                                                                         | Drug is associated with capillary leak syndrome.<br>Patients must have serum creatinine ≤ 1.5 mg/dl prior to treatment.<br>Monitor vital signs and intake and output frequently.<br>(Clinigen, 2019)                                                                                                       |
| Monoclonal antibody: humanized                | Bevacizumab<br>(Avastin®)                  | Nephrotic syndrome, proteinuria                                                             | The drug can cause elevated blood pressure.<br>The drug is associated with proteinuria and increased serum creatinine.<br>(Genentech, 2021b)                                                                                                                                                               |
| Miscellaneous: biologic response modifiers    | Lenalidomide<br>(Revlimid®)                | Hypokalemia, hypomagnesemia, renal failure                                                  | Adjust dose for CrCl < 60 ml/min.<br>Drug is associated with TLS.<br>Use with caution in patients with renal impairment.<br>(Celgene, 2019b)                                                                                                                                                               |

(Continued on next page)

**TABLE 19-1.** Genitourinary Toxicities (*Continued*)

| Classification       | Drug                      | Side Effects and Toxicities                                                                            | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                          |
|----------------------|---------------------------|--------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Miscellaneous</b> |                           |                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                 |
| Bisphosphonates      | Pamidronate (Aredia®)     | Increased serum creatinine, renal insufficiency                                                        | The drug can cause electrolyte abnormalities. For CrCl < 30 ml/min or creatinine > 3 mg/dl, use may be not recommended or dose reduced depending on the disease process. Limited data are available in the setting of dialysis. (Bedford Laboratories, 2009)                                                                                                                    |
|                      | Zoledronic acid (Zometa®) | Increased serum creatinine, renal insufficiency (higher in patients with abnormal baseline creatinine) | Risk of AKI is increased with abnormal baseline creatinine. Monitor serum creatinine before each dose. Do not use doses > 4 ml in patients with renal impairment. Administration over 15 minutes has been associated with reduced renal failure. Limited pharmacokinetic data exist in patients with CrCl < 30 ml/min or with evidence of AKI. (Novartis Pharmaceuticals, 2016) |

AKI—acute kidney injury; CrCl—creatinine clearance; eGFR—estimated glomerular filtration rate; GFR—glomerular filtration rate; min—minute; SIADH—syndrome of inappropriate antidiuretic hormone secretion; TLS—tumor lysis syndrome; ULN—upper limit of normal

## (c) Immunotherapy agents

- i. Interferons and high-dose interleukin-2 induce AKI.
- ii. Immune checkpoint inhibitors, such as ipilimumab, nivolumab, and pembrolizumab, can lead to acute interstitial nephritis.
- iii. Chimeric antigen receptor T cells can cause a capillary leak and subsequent AKI (Rosner et al., 2017).

## (d) Other drugs

- i. Zoledronate, nonsteroidal anti-inflammatory agents, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and iodinated contrast can affect the kidneys (Rosner et al., 2017).
- ii. Antimicrobial drugs, such as aminoglycosides, sulfonamides, and ciprofloxacin; antivirals, such as acyclovir; and antifungals, such as amphotericin B and liposomal formulation, are associated with tubular injury.
- iii. Calcineurin inhibitors used to prevent graft-versus-host disease (GVHD) can induce AKI and thrombotic microangiopathy by promoting arteriolar vasoconstriction (Renaghan et al., 2020).

## (e) HSCT regimens

- i. AKI and long-term renal dysfunction: Myeloablative allogeneic HSCT is associated with the highest risk, followed by nonmyeloablative allogeneic and myeloablative autologous HSCT. Causes include chemotherapy, high-dose radiation accompanied by fluid loss, sepsis, or nephrotoxic drugs used for supportive therapy. Other causes of renal dysfunction in patients receiving HSCT include stem cell infusion toxicity, hepatic sinusoidal obstruction syndrome (or veno-occlusive disease), thrombotic microangiopathy, and GVHD (Kemmner et al., 2017).
- ii. The use of cyclosporine in patients with diabetes mellitus shows a significant association with AKI in the first 100 days following transplant (Renaghan et al., 2020).
- iii. Risk for AKI in nonmyeloablative allogeneic regimens includes diabetes mellitus, more than three cycles of chemotherapy, and methotrexate for GVHD (Renaghan et al., 2020).

## (2) Preexisting conditions



- (a) Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
  - (b) Tumor lysis syndrome
  - (c) Preexisting renal disease
  - (d) Chronic comorbidities (e.g., diabetes, chronic kidney disease [CKD], hypertension, cardiac insufficiency, autoimmune disease)
  - (e) Urinary stones
  - (f) Urinary tract infections
  - (g) Lower urinary tract obstruction
  - (h) Hydronephrosis
  - (i) Neutropenic sepsis
  - (j) Hypercalcemia
  - (k) Volume depletion (e.g., nausea, vomiting, diarrhea)
  - (l) Disseminated intravascular clotting
- (3) Cancer types: hematologic malignancies, especially multiple myeloma, and solid malignancies with renal involvement of tumor (Rosner et al., 2017)
- (4) Patient characteristics
  - (a) Age older than 65 years
  - (b) Family history of CKD
  - (c) Female sex (Rosner et al., 2017)
- d) Clinical manifestations (Perlman & Heung, 2019)
  - (1) Initial symptoms
    - (a) Fatigue
    - (b) Malaise
    - (c) Oliguria: common but not always present with onset of AKI
  - (2) Later symptoms
    - (a) Dyspnea
    - (b) Orthopnea
    - (c) Rales
    - (d) Third heart sounds ( $S_3$ )
    - (e) Peripheral edema
    - (f) Hypertension
    - (g) Altered mental status
    - (h) Weight gain
- e) Assessment
  - (1) Laboratory assessment
    - (a) Serum creatinine must be evaluated along with creatinine clearance, as this level may take 24–72 hours to reflect AKI (Mercado et al., 2019).
    - (b) Creatinine clearance is measured using Cockcroft and Gault estimated creatinine clearance (CG eCRCL) (Sprangers et al., 2021).
    - (c) Urinalysis and microscopy
      - i. Glomerular injury is associated with acanthocytes and red blood cell casts.
      - ii. Drug-induced injury and crystalline nephropathy are associated with crystal casts.
      - iii. Tubulointerstitial injury is associated with leukocyturia, tubular epithelial cells, and granular casts.
      - iv. Ischemic injury is associated with renal tubular epithelial cells and casts, including muddy brown casts (Mercado et al., 2019).
  - (d) Electrolyte abnormalities (urine electrolytes) include azotemia, which can be calculated by excretion of sodium and urea.
  - (e) Albumin
- (2) Imaging: A renal ultrasound is used to evaluate for postrenal causes of AKI.
- (3) Renal biopsy: This procedure is reserved for unclear etiology of AKI (Mercado et al., 2019).
- (4) Physical assessment
  - (a) Intake and output
  - (b) Vital signs
  - (c) Daily weights
  - (d) Edema
  - (e) Costovertebral angle tenderness
- f) Collaborative management
  - (1) Assess for risk factors prior to initiating nephrotoxic agents. Consult with the pharmacy prior to starting any such agents to determine if there is an alternative or if a dose reduction should be considered.
  - (2) Optimize hydration status and evaluation prior to starting therapy.
  - (3) Follow dosing adjustments for patients with impaired renal function.
  - (4) Treat the underlying cause.
  - (5) Monitor for hyperglycemia and consult a clinical nutritionist or registered dietitian for evaluation and planning. Manage comorbid conditions, such as hypertension.
  - (6) Consult with nephrology within 48 hours of initial AKI for lack of response to therapy, unclear etiology, stage 3 or higher AKI, or any other high-risk disease, such as multiple myeloma or in the transplant setting (Mercado et al., 2019).
  - (7) Consider renal replacement therapy for life-threatening conditions, such as anuria, severe hyperkalemia, azotemia with urea concentrations greater than 84 mg/dL,

severe metabolic acidosis, oliguria less than 200 ml over 12 hours, uremia resulting in encephalopathy, neuropathy, pericarditis, and volume overload (Mercado et al., 2019).

g) Patient and family education

- (1) Educate patients and families regarding the risk of AKI with cytotoxic agents.
- (2) Educate patients and families on the signs and symptoms of AKI.
- (3) Instruct patients to notify the healthcare team if the following symptoms occur (Forman, 2021):
  - (a) No urine output for more than 12 hours
  - (b) Very small amounts of dark urine
  - (c) Dark, concentrated, cloudy, or bloody urine
  - (d) Occurrence of edema or acute weight gain
- (4) Encourage patients to monitor their blood pressure at home.
- (5) Educate patients and families about the importance of adequate oral hydration of up to 3 L daily while they are receiving nephrotoxic cytotoxic agents (e.g., cisplatin, methotrexate) (Almanric et al., 2017; Howard et al., 2016).

## 2. SIADH

a) Definition and pathophysiology

- (1) SIADH is a paraneoplastic syndrome characterized by impaired water excretion second to excess antidiuretic hormone, which causes the kidneys to reabsorb water. Water retention, in turn, leads to hyponatremia.
- (2) Paraneoplastic SIADH is thought to result from ectopic secretion of antidiuretic hormone from tumor cells.
- (3) The principle difference between SIADH and cerebral salt wasting is that SIADH occurs in the setting of euvolemia (Kitchlu & Rosner, 2019).

b) Diagnostic criteria (Workeneh et al., 2020)

- (1) Plasma sodium less than 135 mEq/L
- (2) Plasma osmolality less than 275 mOsm/kg
- (3) Urine osmolality greater than 100 mOsm/kg
- (4) Clinical euvolemia
- (5) Urine sodium concentration greater than 30 mmol/L with normal dietary salt and water intake
- (6) Adrenal, thyroid, and renal function to identify contributing causes (Workeneh et al., 2020)

(7) No recent diuretic agents

- c) Incidence: Hyponatremia is the most common electrolyte alteration in patients with cancer. Incidence varies by type of cancer; however, lung cancers are associated with a higher risk (25%–45%) (Kitchlu & Rosner, 2019).

d) Risk factors

(1) Pharmacologic agents

- (a) Chemotherapy: vinka alkaloids (e.g., vincristine, vinblastine), alkylating agents (e.g., cyclophosphamide, ifosfamide), platinum compounds (e.g., cisplatin, carboplatin, methotrexate)
- (b) Immunotherapy: Interferon drugs can cause hypophysitis, an inflammation of the pituitary gland. When the pituitary gland is inflamed, normal body functions can be significantly altered, such as endocrine system regulation and storage of hormones produced by the hypothalamus (Vazquez, 2017).
- (c) Other drugs: amiodarone, amitriptyline, ciprofloxacin, haloperidol, imatinib, nonsteroidal anti-inflammatory drugs, selective serotonin reuptake inhibitors, thiazides

- (2) Preexisting conditions: cerebrovascular accident, infection, mental illness, hypopituitarism, hypothyroidism, HIV (Sterns, 2021)

- (3) Cancer types: small cell lung, prostate, breast, adrenal, head and neck, olfactory neuroblastoma, malignancies with brain involvement (primary or metastatic), malignancies with pulmonary involvement (primary or metastatic) (Workeneh et al., 2020)

- (4) Patient characteristics: age older than 65 years

e) Clinical manifestations: dependent on serum sodium concentration

- (1) Serum sodium 125–135 mEq/L: increased thirst, anorexia, nausea, weakness, fatigue, muscle cramps, headache (Dimitriadis et al., 2017)
- (2) Serum sodium less than 125 mEq/L: altered mental status, seizures, coma, respiratory collapse (Dimitriadis et al., 2017)

f) Assessment

(1) Laboratory assessment

- (a) Serum sodium
- (b) Serum osmolality
- (c) Urine sodium
- (d) Urine osmolality

- (e) Serum cortisol
- (f) Thyroid-stimulating hormone, free thyroxine ( $T_4$ )
- (g) Creatinine clearance
- (2) Imaging: brain magnetic resonance imaging if concern for SIADH secondary to immune-related hypophysitis
- (3) Physical assessment
  - (a) Thorough patient history, including current medications and comorbidities
  - (b) Neurologic examination
  - (c) Assessment for signs and symptoms of fluid volume overload
    - i. Hypertension
    - ii. Edema
    - iii. Weight gain
    - iv. Decreased urine output
    - v. Altered respiratory status
- g) Collaborative management (Kitchlu & Rosner, 2019)
  - (1) Consulting endocrinologists has been shown to improve patient outcomes.
  - (2) Special care must be taken to not over rapidly correct sodium, as this may result in osmotic demyelination syndrome.
    - (a) The general recommendation is to restrict to 500 ml less than daily urine output. The fluid restriction will result in sodium improvements of 2–4 mEq/L daily (Kitchlu & Rosner, 2019).
    - (b) If serum sodium is less than 125 mEq/L or greater than or equal to 125 mEq/L with severe symptoms, raise serum sodium by 4–6 mEq/L over one to two hours, followed by slower correction over 48 hours.
    - (c) Tolvaptan is an antagonist of vasopressin 2 receptor in the distal tubule responsible for free water retention. It is indicated for clinically significant hypovolemic and euvoletic hyponatremia. Consider when serum sodium is not corrected with other therapies or there is a need to correct preprocedure or surgery.
    - (d) Salt tablets
    - (e) Loop diuretics
    - (f) Urea induces osmotic excretion of free water without electrolyte depletion. General dosing is 15–30 g daily or a dose of 0.25–0.50 g/kg.
    - (g) Demeclocycline reduces the loss of sodium in the renal inner medulla; however, efficacy is variable and cannot be routinely recommended.
- (h) If related to hypophysitis, treat with corticosteroids (Vazquez, 2017).
- h) Patient and family education
  - (1) Educate patients and families on the risk factors for SIADH.
  - (2) Educate patients and families on the clinical signs and symptoms of SIADH, and stress the importance of notifying the healthcare team if signs or symptoms appear.
- 3. Tumor lysis syndrome (TLS)
  - a) Definition and pathophysiology
    - (1) TLS is an oncologic emergency that results when many tumor cells are killed (or lysed), causing the intracellular components to be dumped into circulation.
    - (2) This can lead to various metabolic abnormalities, including hyperkalemia, hyperphosphatemia, hypocalcemia, and hyperuricemia, which can cause AKI (Puri et al., 2020).
    - (3) The syndrome is most commonly seen in hematologic malignancies treated with cytotoxic therapies and chemotherapy; however, it can also occur in solid tumors with a significant tumor burden and strong chemosensitivity (Rahmani et al., 2019).
    - (4) Early identification and treatment are critical to avoid life-threatening consequences.
  - b) Diagnostic criteria: Cairo and Bishop (2004) described the most widely accepted definition of TLS with laboratory and clinical considerations. The following laboratory results and clinical data must occur within three days before or seven days after cytotoxic therapy (Cairo & Bishop, 2004).
    - (1) Cairo Bishop laboratory TLS must contain two or more of the following (Cairo & Bishop, 2004; Rahmani et al., 2019):
      - (a) Uric acid 8 mg/dl or higher, or 25% increase from baseline
      - (b) Potassium 6 mEq/L or higher, or 25% increase from baseline
      - (c) Phosphorus 4.5 mg/dl or higher, or 25% increase from baseline
      - (d) Calcium 7 mg/dl or lower, or 25% decrease from baseline
    - (2) Cairo Bishop grading of clinical TLS requires one or more clinical manifestations along with criteria for laboratory TLS. Select the maximal renal, cardiac, or

neurologic clinical TLS manifestation to define the grade.

- (a) Grade 0: creatinine less than or equal to 1.5 times upper limit of normal (ULN)
- (b) Grade 1: creatinine 1.5 times ULN
  - i. Intervention is not indicated for cardiac arrhythmia or seizures in grade 1.
  - ii. Neither creatinine nor cardiac arrhythmia is attributable to chemotherapy agents (Cairo & Bishop, 2004; Rahmani et al., 2019).
- (c) Grade 2: creatinine greater than 1.5–3 times ULN
  - i. Cardiac arrhythmia: nonurgent medical intervention indicated
  - ii. Seizures: one brief generalized seizure and seizures that are well controlled with use of anticonvulsants or focal motor seizures that are infrequent and do not interfere with activities of daily living
  - iii. Neither creatinine, cardiac arrhythmia, or seizure are attributable to chemotherapy agents (Cairo & Bishop, 2004; Rahmani et al., 2019).
- (d) Grade 3: creatinine greater than 3–6 times ULN
  - i. Cardiac arrhythmia: symptomatic and incompletely controlled medically or controlled with a device such as a defibrillator
  - ii. Seizures: may occur where consciousness is altered or is poorly controlled despite medical intervention
  - iii. Neither creatinine, cardiac arrhythmia, or seizure are attributable to chemotherapy agents (Cairo & Bishop, 2004; Rahmani et al., 2019).
- (e) Grade 4: creatinine greater than 6 times ULN
  - i. Cardiac arrhythmia: life threatening (i.e., arrhythmia associated with heart failure, hypotension, syncope, or shock)
  - ii. Seizures: of any kind which are prolonged, repetitive, or difficult to control (i.e., status epilepticus, intractable epilepsy)

- iii. Neither creatinine, cardiac arrhythmia, or seizure are attributable to chemotherapy agents (Cairo & Bishop, 2004; Rahmani et al., 2019).

- (f) Grade 5: Death can be attributable to chronic TLS (Cairo & Bishop, 2004; Rahmani et al., 2019).

c) Incidence: Exact incidence is unknown. TLS remains the most common oncologic emergency in adult and pediatric patients with a hematologic malignancy (Rahmani et al., 2019).

d) Risk factors: Medications, radiation, and steroids cause TLS through rapid cell death. Bulky disease, significant areas of tumor necrosis, highly treatment-sensitive tumors, and those with a highly proliferative rate present an increased risk. TLS can also occur spontaneously without intervention (Rahmani et al., 2019).

(1) Pharmacologic agents

(a) Chemotherapy (e.g., alemtuzumab, cisplatin, cladribine, cytarabine, doxorubicin, etoposide, fludarabine, gemtuzumab, idarubicin, imatinib mesylate, mitoxantrone, paclitaxel, rituximab, tamoxifen)

(b) Radiation (e.g., total body irradiation)

(c) Other drugs (e.g., corticosteroids)

(2) Cancer types, rate of differentiation (acute vs. chronic), degree of white blood cell (WBC) and lactate dehydrogenase (LDH) elevation, age, comorbid conditions, and cancer therapy should be taken into account when determining the risk of TLS (Rahmani et al., 2019).

(a) Cancers associated with a higher risk of developing TLS are defined as a greater than 5% risk and include the following (Rahmani et al., 2019):

i. Leukemias

- Any Burkitt leukemia
- Acute lymphoblastic leukemia with a WBC count greater than or equal to 100,000/mm<sup>3</sup> or serum LDH level greater than or equal to two times ULN
- Acute myeloid leukemia with WBC count greater than or equal to 100,000/mm<sup>3</sup>
- Chronic lymphocytic leukemia with bulky features: greater than or equal to 10 cm or lymph nodes greater

- than or equal to 5 cm, absolute lymphocyte count greater than or equal to 25,000/mm<sup>3</sup>, elevated uric acid
- ii. Lymphomas
  - Advanced stage Burkitt lymphoma or lymphoblastic lymphoma or early stage for either with LDH two times ULN
  - Adult T-cell, diffuse large B-cell, peripheral T-cell, transformed, or mantle cell lymphomas with elevated LDH and significant tumor burden
  - Pediatric stage III–IV diffuse large B-cell lymphoma with LDH greater than or equal to two times ULN
- (b) Cancers associated with an intermediate risk of developing TLS (1%–5%) include the following (Rahmani et al., 2019):
  - i. Leukemias
    - Acute lymphoblastic leukemia with WBC count less than 100,000/mm<sup>3</sup> or serum LDH level less than two times ULN
    - Acute myeloid leukemia with WBC 25,000–100,000/mm<sup>3</sup>
  - ii. Bulky solid tumors sensitive to chemotherapy, including neuroblastoma, germ cell cancer, and small cell lung cancer
  - iii. Lymphomas
    - Adult T-cell, diffuse large B-cell, peripheral T-cell, transformed, or mantle cell leukemias or early-stage Burkitt type with LDH two times ULN
    - Pediatric stage III–IV anaplastic large cell lymphoma with LDH greater than or equal to two times ULN
    - Early-stage lymphoblastic lymphomas with LDH less than two times ULN
  - iv. Chronic lymphocytic leukemia and small lymphocytic lymphomas present a risk in the setting of lymph nodes greater than or equal to 5 cm or an absolute lymphocyte count greater than or equal to 25,000/mm<sup>3</sup> or a WBC greater than or equal to 50,000/mm<sup>3</sup> and treated with fludarabine, rituximab, lenalidomide, or venetoclax.
- (c) Cancers associated with a low risk of developing TLS (less than 1%) include the following (Rahmani et al., 2019):
  - i. Acute myeloid leukemia with WBC less than 25,000/mm<sup>3</sup> and serum LDH less than two times ULN
  - ii. Chronic lymphocytic leukemias and small lymphocytic lymphomas with WBC less than or equal to 50,000/mm<sup>3</sup> without any treatment with fludarabine, rituximab, or venetoclax
  - iii. Multiple myeloma and chronic myeloid leukemia
  - iv. Any other non-Hodgkin lymphoma with normal LDH and any other solid tumor
- (3) Patient characteristics may include acidic urine, dehydration, extensive lymph node involvement, hyperuricemia, increased LDH, leukocytosis, hyperkalemia, hyperphosphatemia, large tumor burden, nephrotoxic agent exposure, oliguria, renal dysfunction, and renal involvement of cancer at diagnosis (Kaplow & Iyere, 2016).
- e) Clinical manifestations resulting from metabolic abnormalities (Klemencic & Perkins, 2019; Rahmani et al., 2019)
  - (1) Weakness
  - (2) Nausea and vomiting
  - (3) Diarrhea
  - (4) Electrocardiogram abnormalities
  - (5) Muscle twitching
  - (6) Confusion and delirium
  - (7) Seizures
  - (8) Peripheral edema
  - (9) Oliguria and hematuria
  - (10) Flank pain
  - (11) Paralysis
  - (12) Paresthesias
  - (13) Muscle cramps
- f) Assessment
  - (1) Laboratory assessment: complete blood count, comprehensive metabolic panel,

magnesium, phosphorus, uric acid, LDH, urinalysis, arterial blood gases, creatinine clearance (using Cockcroft-Gault formula)

(2) Imaging: electrocardiogram

(3) Physical examination

(a) Vital signs

(b) Chvostek sign: contraction of the ipsilateral facial muscles elicited by tapping the facial nerve just in front of the ear (Goltzman, 2021)

(c) Trousseau sign: adduction of the thumb, flexion of wrist and metacarpophalangeal joints, and extension of the interphalangeal joints as induced by a blood pressure cuff inflated above systolic blood pressure on the upper arm for three minutes (Goltzman, 2021)

(d) Weight changes

(e) Daily intake and output

(f) Changes in mental status

g) Collaborative management

(1) Prevention: Close monitoring and assessment of high-risk patients are essential to prevent and treat TLS (Puri et al., 2020).

(2) Treatment and management: A combination of monitoring, hydration, and hypouricemic therapy are essential for prevention, management, and treatment (Puri et al., 2020).

(a) Hydration

i. General recommendations include 2–3 L/m<sup>2</sup> of IV crystalloids daily to promote glomerular filtration and subsequent urine output. Urine output should generally be maintained at 70–100 ml/m<sup>2</sup> per hour. IV hydration can be discontinued when LDH normalizes or with resolution of tumor burden. Volume status and comorbid conditions must be considered (Puri et al., 2020).

ii. Diuretics may be considered to maintain adequate urine output after hypovolemia and obstructive uropathy are ruled out (Puri et al., 2020).

(b) Alkalinization: The role of alkalization is controversial given the risk of calcium phosphate precipitation, worsening kidney function, and hypocalcemia (Puri et al., 2020).

(c) Allopurinol

i. Prevents the conversion of purine metabolites to uric acid

ii. Used in combination with vigorous hydration in low-risk patients (Shaikh et al., 2018) and is the drug of choice in intermediate-risk patients (Puri et al., 2020)

iii. Allopurinol oral dosing: 100 mg/m<sup>2</sup> every eight hours (maximum 800 mg daily) in adults (Puri et al., 2020)

(d) Recombinant urate oxidase (rasburicase)

i. The U.S. Food and Drug Administration approved rasburicase in 2002 to manage TLS. Rasburicase works by rapidly reducing uric acid levels to prevent or reverse AKI (Shaikh et al., 2018).

ii. Rasburicase is used in high-risk patients and is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency. Side effects include methemoglobinemia, hemolysis, and anaphylaxis (Puri et al., 2020).

iii. Dosing is a 6 mg flat dose; however, recent evidence has suggested a 3 mg flat dose is noninferior for patients with uric acid levels of 8–15 mg/dl (Shaikh et al., 2018).

(3) Nursing considerations

(a) Monitor for cardiac arrhythmias.

(b) Closely monitor laboratory results, specifically paying attention to electrolytes, uric acid, and renal function.

(c) Ensure adequate hydration of at-risk patients.

(d) Closely monitor for changes in cognition or mental status.

h) Patient and family education

(1) Educate patients and families on the risk factors and treatment strategies for TLS.

(2) Educate patients and families on the clinical signs and symptoms of TLS and stress the importance of notifying the healthcare team if these appear.

4. CKD (see Figure 19-2)

a) Definition and pathophysiology



**FIGURE 19-2.** Chronic Kidney Disease Nomenclature

**CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE  
USED BY KDIGO**

CKD is defined as abnormalities of kidney structure or function present for > 3 months, with implications for health and CKD is classified based on cause, GFR category, and albuminuria category (CGA).

**Prognosis of CKD by GFR and albuminuria category**

| Prognosis of CKD by GFR<br>and Albuminuria Categories:<br>KDIGO 2012  |     |                                  |       | Persistent albuminuria categories<br>Description and range |                             |                          |
|-----------------------------------------------------------------------|-----|----------------------------------|-------|------------------------------------------------------------|-----------------------------|--------------------------|
|                                                                       |     |                                  |       | A1                                                         | A2                          | A3                       |
|                                                                       |     |                                  |       | Normal to mildly increased                                 | Moderately increased        | Severely increased       |
|                                                                       |     |                                  |       | <30 mg/g<br><3 mg/mmol                                     | 30–300 mg/g<br>3–30 mg/mmol | >300 mg/g<br>>30 mg/mmol |
| GFR categories (ml/min/1.73 m <sup>2</sup> )<br>Description and range | G1  | Normal to high                   | ≥ 90  |                                                            |                             |                          |
|                                                                       | G2  | Mildly decreased                 | 60–89 |                                                            |                             |                          |
|                                                                       | G3a | Mildly to moderately decreased   | 45–59 |                                                            |                             |                          |
|                                                                       | G3b | Moderately to severely decreased | 30–44 |                                                            |                             |                          |
|                                                                       | G4  | Severely decreased               | 15–29 |                                                            |                             |                          |
|                                                                       | G5  | Kidney failure                   | <15   |                                                            |                             |                          |

|  |                                                          |  |                           |  |           |  |                |
|--|----------------------------------------------------------|--|---------------------------|--|-----------|--|----------------|
|  | low risk (if no other markers of kidney disease, no CKD) |  | moderately increased risk |  | high risk |  | very high risk |
|--|----------------------------------------------------------|--|---------------------------|--|-----------|--|----------------|

Note. From "KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease," by Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2012, *Kidney International Supplements*, 3(1), p. x ([https://kdigo.org/wp-content/uploads/2017/02/KDIGO\\_2012\\_CKD\\_GL.pdf](https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf)). Copyright 2013 by KDIGO. Reprinted with permission.

- (1) CKD is defined as abnormalities of kidney structure or function, present for longer than three months, with health implications. It is classified based on cause, GFR category, and albuminuria category (International Society of Nephrology, 2013).
- (2) CKD is further distinguished by the irreversible loss of nephrons with subsequent glomerular sclerosis characterized by fibrotic changes to remaining nephrons.
- (3) Clinical sequela of the disease state is a determinant of the stage of the disease, with later stages being more severe.
- (4) Given the complex role of the kidney in maintaining homeostasis, CKD is characterized as a systemic disease.
- (5) Uremia results in retention of otherwise normally excreted products, a rise in physiologic hormones, and an overall loss in kidney function, such as erythropoietin production (Perlman & Heung, 2019).
- (6) Reductions in GFR lead to sodium and water retention and the lack of potassium excretion, resulting in hypertension, edema, heart failure, and life-threatening arrhythmias.



- (7) Metabolic acidosis occurs second to the diminished ability to generate bicarbonate and excrete acid.
  - (8) Significant risk for osteomalacia of the bones occurs due to decreased production of vitamin D. Elevated levels of phosphorus, coupled with decreased absorption of calcium, results in overcompensation by the parathyroid to resorb calcium from bones.
  - (9) Decreased erythropoietin production results in anemia, and uremic toxins suppress platelet aggregation and leukocyte function.
  - (10) A cascade of skin changes occurs related to pigmented metabolites.
  - (11) Decreases in estrogen and testosterone from uremic products may result in amenorrhea and overall infertility (Perlman & Heung, 2019).
  - b) Incidence: CKD in patients with cancer occurs with a prevalence rate of 12%–53% upon initial diagnosis (Sprangers et al., 2019).
  - c) Risk factors
    - (1) Chemotherapy: cisplatin, ifosfamide, melphalan, methotrexate, vinblastine, vincristine, vinorelbine
    - (2) Preexisting conditions: diabetes, hypertension, cardiovascular disease, HIV, hepatitis C virus, malignancy, autoimmune diseases, nephrolithiasis, recurrent urinary tract infections, family history of renal disease (Ammirati, 2020)
    - (3) Cancer types: solid tumor malignancies, multiple myeloma, bone metastasis
    - (4) Patient characteristics
      - (a) Age older than 70 years
      - (b) Male sex
      - (c) Cigarette use
  - d) Clinical manifestations
    - (1) Hypertension
    - (2) Edema
    - (3) Weight gain
    - (4) Decreased urine output
  - e) Assessment
    - (1) Laboratory assessment (Ammirati, 2020)
      - (a) Serum creatinine
      - (b) Blood urea nitrogen
      - (c) Creatinine clearance using Cockcroft-Gault formula or 24-hour urine (Cockcroft & Gault, 1976)
      - (d) Proteinuria: best assessed with 24-hour urine
      - (e) Comprehensive metabolic panel: calcium, phosphorus, alkaline phosphatase
    - (f) Albumin
    - (g) Complete blood count
    - (h) Parathyroid hormone
    - (i) Vitamin D
    - (j) Venous blood gas
    - (k) Lipids
    - (l) Virology studies: hepatitis B
  - (2) Imaging: renal ultrasound, echocardiogram, electrocardiogram
  - (3) Physical assessment
    - (a) Intake and output
    - (b) Vital signs
    - (c) Daily weights
    - (d) Edema
    - (e) Costovertebral angle tenderness
  - f) Collaborative management
    - (1) Patients with preexisting CKD should be followed by a nephrologist while undergoing cancer treatment.
    - (2) Criteria for referral include GFR less than 30 ml/min/1.73 m<sup>2</sup>, a decrease greater than or equal to 25% in the GFR, progression of CKD with a yearly decrease of more than 5 ml/min, significant albuminuria, persistent hematuria without a clear cause, persistent metabolic acidosis, anemia of CKD, resistant hypertension, recurrent nephrolithiasis, or hereditary kidney disease (Ammirati, 2020).
    - (3) Renal replacement therapy should be considered with a GFR less than 20 ml/min and with progressive disease.
    - (4) Procedural therapeutics, such as peritoneal or hemodialysis, should be determined on an individualized basis according to risks and benefits (Ammirati, 2020).
  - g) Patient and family education
    - (1) Educate patients and families regarding CKD risk with cytotoxic agents.
    - (2) Educate patients and families on the signs and symptoms of worsening CKD and the treatment goals to slow CKD progression and manage comorbid conditions.
    - (3) Encourage patients to monitor their blood pressure at home.
    - (4) Educate patients and families on the importance of continued follow-up with a nephrologist while undergoing cancer treatment.
5. Hemorrhagic cystitis
- a) Definition and pathophysiology
    - (1) Hemorrhagic cystitis is a diffused inflammatory condition of the urinary bladder due to an infection or noninfectious etiology, resulting in bleeding from

the bladder mucosa (Manikandan et al., 2010).

- (2) Treatment-related causes include chemotherapy and pelvic radiation (Dautruche & Delouya, 2018).
- (3) Although bacteria and fungi pathogens promote inflammation of the urinary tract, they seldom cause hemorrhagic cystitis.
- (4) Viruses have a high incidence of causing hemorrhagic cystitis in immunocompromised patients.
- (5) Hemorrhagic cystitis can be acute or chronic. The severity can range from mild discomfort in the lower abdomen to severe life-threatening hemorrhage characterized by urinary frequency, lower abdominal pain, and dysuria (Dosin et al., 2017; Schneidewind et al., 2018).

#### b) Incidence

- (1) Hemorrhagic cystitis may affect up to 70% of the immunocompromised population and up to 66% of HSCT recipients (Cesaro et al., 2018; Ruggeri et al., 2015).
- (2) BK virus occurs in 50% of HSCT recipients and can lead to BK polyomavirus-associated hemorrhagic cystitis in up to 20% (Atilla et al., 2020).
- (3) The incidence of hemorrhagic cystitis in the adult and pediatric population after HSCT ranges from 10% to 70% in the literature (Au et al., 2017; Cesaro et al., 2018).
- (4) Early-onset hemorrhagic cystitis, occurring as early as 48 hours after HSCT conditioning, is usually associated with thrombocytopenia, conditioning regimens with high-dose alkylating chemotherapy agents, and radiation therapy. Delayed-onset hemorrhagic cystitis occurs between two weeks and six months post-transplant, is usually caused by viral infections due to depressed immune cell response or GVHD, and is often fatal (Au et al., 2017; Cesaro et al., 2018).

#### c) Risk factors

##### (1) Pharmacologic agents

- (a) Chemotherapy agents are known to cause hemorrhagic cystitis due to hepatic breakdown of antineoplastic agents to toxic compounds that affect the internal membrane of the bladder or urothelium (Johnston et al., 2015).
  - i. Cyclophosphamide and ifosfamide are metabolized by the

liver and converted into anti-neoplastic agents, such as nitrogen mustard, and phosphoramide mustard, respectively, and into a compound called acrolein responsible for injury to the urothelium in the bladder (Almalag et al., 2021; Matz & Hsieh, 2017). Accumulation of acrolein in the bladder induces the release of inflammatory mediators, including tumor necrosis factor-alpha, interleukin-1-beta, and endogenous nitric oxide. This provokes vascular dilation, mucosal inflammation, and increased capillary fragility, causing bladder mucosal ulceration and hemorrhage (Matz & Hsieh, 2017).

- ii. Busulfan and thiotepea are alkylating agents known to induce trauma to the urothelium wall of the bladder. These are often used in the conditioning regimen for HSCT (Lam et al., 2017).

(b) Pelvic radiation therapy, with or without chemotherapy, causes hemorrhagic cystitis in patients with cancer (Halder et al., 2014). The effect of high-energy radiation can cause cell death through DNA damage and increased permeability of cell membranes, leading to activation of DNA damage repair genes and apoptosis in a continuous cycle that depletes the energy sources of the cells and results in loss of bladder muscle expansion, hyperplasia, and progressively worsening hemorrhagic cystitis (Halder et al., 2014; Zwaams et al., 2018).

- i. External beam radiation causes tissue damage, resulting in impaired healing and necrosis of the bladder mucosa. Telangiectasia (permanent dilation of blood vessels, usually in the mucous membranes) develops and can cause bleeding and pain (Zwaams et al., 2018).
- ii. Radiation causes cellular depletion, fibrosis, and oblit-

erative endarteritis (inflammation of the inner lining of the artery) of the urothelial wall in the bladder, resulting in atrophy and fibrosis and causing late-onset hemorrhagic cystitis (Thompson et al., 2014; Zwaams et al., 2018).

(2) Preexisting conditions

(a) GVHD, a complication after HSCT, is a condition in which the matured T cells from the transplant attack the host tissues of the recipient.

i. GVHD in the bladder may also cause hemorrhagic cystitis as T lymphocytes induce urothelial damage and hematuria (Lunde et al., 2015; Peterson et al., 2016).

ii. Immunosuppressive therapies to treat GVHD aid in microorganism infections that exacerbate hemorrhagic cystitis (Lunde et al., 2015; Raaijmakers, 2021).

(b) Infection may lead to hemorrhagic cystitis by acquired or reactivation of microorganisms in a sustained immunocompromised state (Peterson et al., 2016; Schneidewind et al., 2017).

i. BK virus, JC virus, adenovirus type 11, cytomegalovirus, and herpesvirus play a crucial role in inflammatory processes and breakdown of the bladder mucosa epithelial cells, leading to painful hematuria in patients with cancer (Atilla et al., 2020; Dosin et al., 2017).

ii. Fungal organisms, such as *Candida albicans*, *Candida tropicalis*, *Cryptococcus neoformans*, *Aspergillus fumigatus*, and *Torulopsis glabrata*, cause inner bladder inflammation and damage to the urothelium in the bladder (Cesaro et al., 2018; Pappas et al., 2016).

iii. Bacterial infections affecting the bladder mucosa, specifically *Escherichia coli*, *Staphylococcus saprophyticus*, *Proteus mirabilis*, and *Klebsiella*,

contribute to the loss of cellular urothelial protective function in the bladder (Cesaro et al., 2018).

d) Clinical manifestations

(1) Signs and symptoms of patients presenting with hemorrhagic cystitis should be classified based on the bleeding grade to provide a prognosis of survival and treatments. Grading ranges from 1 to 4; a higher grade indicates a higher mortality risk (Au et al., 2017).

(a) Grade 1: presenting microscopic hematuria

(b) Grade 2: macroscopic hematuria

(c) Grade 3: macroscopic hematuria with small clots

(d) Grade 4: gross hematuria with clots causing urinary tract obstruction requiring clot evacuation

(2) The *Common Terminology Criteria for Adverse Events* uses grading criteria based on the level of intervention required for therapy (National Cancer Institute Cancer Therapy Evaluation Program, 2017; see Table 19-2).

(3) In addition to the severity of bleeding, hemorrhagic cystitis is classified according to the time of occurrence after cancer treatments.

(a) Early stage is within 48 hours.

(b) Late stage is after the first 72 hours post-treatment.

(c) Patients may present with late-stage hemorrhagic cystitis two to three weeks after initial treatment.

(d) Patients experiencing hemorrhagic cystitis may present with pain in the lower abdominal area, fever, weakness, palpitations, and frustration due to the prolonged period of discomfort (Au et al., 2017; Dosin et al., 2017).

e) Assessment

(1) Review past infections that a neutropenic state or immunosuppression may reactivate to prevent GVHD, such as BK virus (Graham, 2017; Karagun et al., 2021).

(2) Collaborate with medical teams to expedite obtaining urine culture and polymerase chain reaction to identify pathogen infections and viral load (Klein et al., 2015).

(3) Assess renal function by obtaining laboratory levels of GFR, blood urea nitrogen,

**TABLE 19-2.** Common Terminology Criteria for Adverse Events Grading for Cystitis Noninfective

| Adverse Event         | Grade                                                                                                          |                                                                                                                                                                                                               |                                                                                                                               |                                                              |       |
|-----------------------|----------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|-------|
|                       | 1                                                                                                              | 2                                                                                                                                                                                                             | 3                                                                                                                             | 4                                                            | 5     |
| Cystitis noninfective | Microscopic hematuria; minimal increase in frequency, urgency, dysuria, or nocturia; new onset of incontinence | Moderate hematuria; moderate increase in frequency, urgency, dysuria, nocturia, or incontinence; urinary catheter placement or bladder irrigation indicated; limiting instrumental activities of daily living | Gross hematuria; transfusion, intravenous medications, or hospitalization indicated; elective invasive intervention indicated | Life-threatening consequences; urgent intervention indicated | Death |

Note. From *Common Terminology Criteria for Adverse Events* [v.5.0], by National Cancer Institute Cancer Therapy Evaluation Program, 2017 ([https://ctep.cancer.gov/protocoldevelopment/electronic\\_applications/docs/CTCAE\\_v5\\_Quick\\_Reference\\_5x7.pdf](https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf)). In the public domain.

creatinine, and urinalysis. Collaborate in obtaining an interstitial biopsy to verify and monitor bladder and renal infections (Cesaro et al., 2018; Klein et al., 2015).

- (4) Identify drinking and voiding patterns to formulate plans of care in the presence of possible hemorrhagic cystitis.
- (5) Assess menstrual cycle to prevent misinterpretation with hematuria.
- (6) Review treatment plans to correlate potential risk factors for hemorrhagic cystitis, including chemotherapy agents, radiation therapy, pathogen infections, and neutropenia. Identify antineoplastic therapies associated with hemorrhagic cystitis (e.g., cyclophosphamide, ifosfamide, radiation) and monitor for clinical manifestations.

f) Monitoring

- (1) Monitor urinalysis to identify possible occurrences of hematuria (Thompson, 2017).
- (2) Monitor urinalysis and sensitivity to screen for potential pathogens associated with hemorrhagic cystitis (Thompson, 2017).
- (3) Monitor complete blood count to anticipate risks of anemia, neutropenia, and thrombocytopenia in the presence of hemorrhagic cystitis (Cesaro et al., 2018; Thompson, 2017; Wilkinson et al., 2015).
- (4) Monitor fluid intake and output to maintain fluid balance at all times (Thompson, 2017).

g) Treatment: Management of hemorrhagic cystitis varies depending on etiology and symptom-

atic presentation. Some antineoplastic protocols include initiating continuous bladder irrigation in the presence of conditioning regimens known to cause hemorrhagic cystitis.

- (1) Bladder irrigation: Manual or continuous bladder irrigation remains a treatment of choice for hemorrhagic cystitis. A three-way urethral catheter that allows manual piston saline irrigation or continuous bladder irrigation will decompress any clots formed and often stop the bleeding (Yang et al., 2020). In addition, continuous bladder irrigation decreases the concentration of acrolein and its contact time with the bladder urothelium. Some antineoplastic protocols include initiating it prior to cyclophosphamide chemotherapy or in combination with the bladder protectant mesna, hyperhydration with forced diuresis and frequent voiding, antibiotic prophylaxis with fluoroquinolones, and urethral catheterization (Gonella et al., 2015; Yang et al., 2020).

- (a) Continuous bladder irrigation with 0.9% sodium chloride isotonic solution or manual irrigation of clots reduces bleeding by removing urokinase, an anticoagulant substance secreted into the urine by the kidney (Gonella et al., 2015; Yang et al., 2020). Continuous bladder irrigation has not been shown in recent studies to decrease the incidence of hemorrhagic cystitis but did decrease the duration of hemorrhagic cystitis (Cesaro et al., 2018).

- (b) Alum may be added to bladder irrigation to cause reduced protein precipitation, vasoconstriction, and decreased capillary permeability (Ziegelmann et al., 2017).
  - (c) Silver nitrate bladder instillation causes chemical coagulation and scarring at the bleeding site (Ziegelmann et al., 2017).
  - (d) Formalin bladder instillation stops bleeding by causing chemical corrosion in the bladder mucosa without scar tissue formation (Ziegelmann et al., 2017).
- (2) 2-Mercaptoethane sodium sulfonate (mesna) is the most widely used uroprotective agent that neutralizes the corrosive metabolite acrolein, which is responsible for the induction of hemorrhagic cystitis. Different dosages and timings of mesna and hyperhydration have been tested as prophylaxis against hemorrhagic cystitis. In 2008, the American Society of Clinical Oncology updated clinical practice guidelines for the use of mesna (Hensley et al., 2009).
- (a) Mesna dosing with ifosfamide therapy
    - i. With a standard dose of ifosfamide less than 2.5 g/m<sup>2</sup> daily, mesna dosing should equal 60% of the total daily dose of ifosfamide and be divided between three bolus doses administered 15 minutes before and four and eight hours after the administration of each dose of ifosfamide (Hensley et al., 2009; Matz & Hsieh, 2017).
    - ii. For an ifosfamide dosage greater than 2.5 g/m<sup>2</sup> daily, mesna dosing has not been established, although it has been given in divided doses equivalent to 60%–160% of the ifosfamide daily dose. An example regimen includes the following:
      - Before ifosfamide: mesna equivalent of 20% of the total daily ifosfamide dose given as IV bolus
      - During ifosfamide: mesna equivalent of 100%–120% of the total daily ifosfamide dose given as IV infusion over 24 hours (mixed in bags with ifosfamide)
      - After ifosfamide: mesna equivalent of 60% of the total daily ifosfamide dose given as IV infusion over 12 hours
      - Alternatively, mesna can be administered via IV at a dose equivalent to 20% of the ifosfamide dosage, followed by two oral doses, each equivalent to 40% of the antineoplastic agent. Mesna oral doses should be administered two and six hours after each dose of ifosfamide (Hensley et al., 2009).
  - (b) Mesna dosing with cyclophosphamide therapy
    - i. Mesna dosing with high-dose cyclophosphamide (greater than 1 g/m<sup>2</sup>; HSCT mobilization with cyclophosphamide 1.5 g/m<sup>2</sup>) requires mesna equivalent to 60%–160% of the total dose of cyclophosphamide daily given via IV. Mesna must be given by IV administration in three to five divided doses or by continuous infusion. Mesna should be administered each day cyclophosphamide is administered and continued for at least 24 hours after cyclophosphamide is discontinued (Hensley et al., 2009).
    - ii. Post-transplant cyclophosphamide can be used as a therapy to prevent GVHD and graft failure in haplo-identical HSCT. Given the increased risk of more severe cases of hemorrhagic cystitis in this population, mesna and hyperhydration have also been used as preventive strategies. Although insufficient evidence exists to suggest an optimal dose and administration schedule, IV mesna at 20 mg/kg bolus every three hours for

a total of 16 doses (equivalent to 320% of the total daily dose of cyclophosphamide) resulted in a lower incidence of hemorrhagic cystitis when compared to other studies (Mac et al., 2021).

iii. Mesna administration

- Mesna can be given by mouth, considering its bioavailability and half-life are approximately 50% of those observed after IV infusion (Jeelani et al., 2017).
- In patients receiving cyclophosphamide for HSCT, mesna plus saline diuresis is recommended to prevent hemorrhagic cystitis (Matz & Hsieh, 2017).

(c) Hyperbaric oxygen therapy may be used, as it causes vasoconstriction, enhances angiogenesis and granulation tissue formation, and optimizes immune function at the cellular level to the urothelial mucosa (Cesaro et al., 2018; Dautruche & Delouya, 2018).

(d) Surgical interventions

- i. Cystoscopy and fulguration using high-frequency energy channeled via electrocautery or laser
- ii. Intravesical formalin instillation using a large-bore catheter and cystogram under general anesthesia (Ziegelmann et al., 2017)
- iii. Cystectomy with urinary diversion (Au et al., 2017)

(3) Care coordination: Coordinate care with social work services, case management, home health, and pharmacy for patients undergoing hemorrhagic cystitis treatment.

h) Patient and family education

- (1) Educate patients and caregivers about the importance of actively participating in preventing and managing hemorrhagic cystitis.
- (2) Explain the importance of oral hydration, if not contraindicated, to stimulate frequent voiding while receiving oncologic treatments. Polyuria minimizes the time that acrolein and microorganisms are in the bladder.

(3) Teach patients and families neutropenic precautions to avoid new and recurrent infections that may exacerbate hemorrhagic cystitis during the recovery state.

(4) Educate about the importance of assessing urine and symptoms associated with hemorrhagic cystitis (e.g., pink and dark color, burning sensation while voiding, difficulty voiding, lack of sensation to urinate, frequency, lower abdomen pain).

(5) Explain to patients and caregivers continuous bladder irrigation and symptom management (Thompson, 2017; Wilkinsson et al., 2015).

C. Drug-specific considerations

1. Chemotherapy

a) Cisplatin is a platinum-based antineoplastic agent used in many different malignancies. Nephrotoxicity is the primary dose-limiting toxicity, and thus treatment with cisplatin-based regimens necessitates careful evaluation, prevention, and management of associated nephrotoxicity (Crona et al., 2017). Although multiple mechanisms of injury exist, rapid distribution into the kidneys, particularly increased concentration of cisplatin in the tubules, may account for such toxicity (Dahal et al., 2016). Cisplatin can also cause SIADH, salt wasting, magnesium wasting, and hypokalemia, leading to nephrotoxicity (Almanric et al., 2017).

(1) Incidence

(a) In a landmark article on cisplatin toxicity, approximately 28%–36% of patients treated with cisplatin therapy experience nephrotoxicity and 20% can be severe (Yao et al., 2007).

(b) Data on incidence are limited because studies use different renal evaluation metrics, such as serum creatinine, estimated GFR, and creatinine clearance.

(c) A recent meta-analysis comparing cisplatin-based to non-cisplatin-based regimens sought to determine the best method for measuring the true nephrotoxicity of cisplatin. Results revealed the incidence of nephrotoxicity when measured by serum creatinine alone was 1.82% for the cisplatin group compared to 0.23% for the non-cisplatin group.

(d) The incidence of severe nephrotoxicity, when measured by creatinine



clearance, was 1.09% in the cisplatin group compared to 0.72% in the non-cisplatin group.

- (e) In studies where either method was used, the incidence of severe nephrotoxicity was 0.88% with cisplatin-containing regimens and 0.45% with non-cisplatin regimens. This study suggested that using creatinine alone compared to metrics that estimate renal function, such as estimated GFR and creatinine clearance, can result in higher nephrotoxicity. Thus, estimated GFR or creatinine clearance would be the preferred evaluation metric in future studies. (Dahal et al. 2016).
  - (2) Risk factors (Almanric et al., 2017)
    - (a) Pharmacologic agents
      - i. Chemotherapy: previous cisplatin exposure
      - ii. Other agents: angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, hydrochlorothiazide
    - (b) Preexisting conditions: hypertension, arteriosclerotic heart disease, myocardial infarction, coronary artery bypass surgery, type 2 diabetes
    - (c) Patient characteristics: hypomagnesemia, hypokalemia
  - (3) Clinical manifestations
    - (a) Hypertension
    - (b) Electrolyte disturbances
    - (c) Edema
  - (4) Assessment: Assess creatinine clearance using the Cockcroft-Gault formula prior to cisplatin administration.
  - (5) Collaborative management
    - (a) For hydration, patients should receive 2–4 L of normal saline over two to six hours with cisplatin administration (Crona et al., 2017; Duffy et al., 2018).
    - (b) Mannitol reduces the concentration of cisplatin in the kidneys; some studies suggest it should only be used for high-dose cisplatin (100 mg/m<sup>2</sup>) or with preexisting hypertension (Crona et al., 2017; Duffy et al., 2018).
    - (c) Electrolytes, specifically magnesium and potassium, should be monitored; add to IV hydration accordingly (Duffy et al., 2018).
- b) Methotrexate is an antimetabolite chemotherapy drug that disrupts folic acid metabolism and is used for different malignancies. AKI is a well-documented toxicity, and methotrexate, as with cisplatin, requires close monitoring and prompt intervention to avoid kidney damage (Howard et al., 2016). Nephrotoxicity occurs through crystal nephropathy, resulting from methotrexate and its metabolites forming precipitate within the renal tubules. Crystal-induced nephropathy initially might cause an elevation in serum creatinine and then progress to tubular necrosis (Howard et al., 2016; Sales & Foresto, 2020).
    - (1) Incidence: Doses greater than 500 mg/m<sup>2</sup> are associated with a 2%–12% incidence of AKI (Howard et al., 2016).
    - (2) Risk factors
      - (a) Pharmacologic agents
        - i. Chemotherapy: high-dose methotrexate dosing
        - ii. Other agents: concurrent use of drugs that impair methotrexate clearance, such as non-steroidal anti-inflammatory drugs, penicillin, salicylates, probenecid, gemfibrozil, trimethoprim-sulfamethoxazole, proton pump inhibitors, levetiracetam, amphotericin, aminoglycosides, and radiographic contrast dyes (Howard et al., 2016)
      - (b) Preexisting conditions: history of nephrotoxicity with previous methotrexate therapy
      - (c) Cancer types: lymphomas
      - (d) Patient characteristics: volume depletion
    - (3) Clinical manifestations
      - (a) Edema
      - (b) Electrolyte disturbances
      - (c) Hypertension
    - (4) Assessment
      - (a) Laboratory assessment
        - i. Monitor blood urea nitrogen and creatinine.
        - ii. Monitor urine pH and maintain greater than 7.
      - (b) Physical assessment
        - i. Assess for signs and symptoms of fluid overload.
        - ii. Perform strict intake and output monitoring.
    - (5) Collaborative management (Howard et al., 2016)



- (a) Discontinue medications that interfere with methotrexate elimination.
- (b) For hydration, administer prehydration with IV fluids containing bicarbonate at a rate of 150–200 ml/hr up to 2 L prior to high-dose methotrexate administration (Howard et al., 2016).
- (c) Perform strict monitoring of intake and output during and after high-dose methotrexate infusion.
- (d) Because methotrexate and its metabolites are poorly soluble in an acidic pH, using sodium bicarbonate for hydration increases urine pH to 7 and thus increases the solubility of methotrexate, minimizing the risk of intratubular crystal formation (Howard et al., 2016).
- (e) Monitor plasma methotrexate levels closely and adjust leucovorin dosing accordingly.
- (f) Glucarpidase is the antidote for methotrexate and is indicated only for toxic methotrexate plasma concentrations greater than 1  $\mu\text{mol/L}$  in patients with delayed clearance due to renal impairment (Ramsey et al., 2018).

## 2. Immunotherapy

- a) Immune checkpoint inhibitors, first approved for melanoma, have quickly emerged in treatment of several neoplasms. They work by enhancing tumor-directed immune response by targeting inhibitory receptors seen on T cells and other tumor cells (Cortazar et al., 2016). The toxicities associated with immunotherapy agents are immune-related events with cytotoxic T-lymphocyte-associated protein inhibitors (e.g., ipilimumab) and programmed cell death-ligand 1 inhibitors (e.g., nivolumab, pembrolizumab) causing interstitial nephritis and glomerulonephritis (Sales & Foresto, 2020).
- b) Management: Although no standard of care exists for immune-related nephritis, as with other immune-related toxicities, it is typically managed with steroids (Cortazar et al., 2016; Izzedine et al., 2014; Thajudeen et al., 2015). Once immune-related etiology is confirmed, usually via biopsy, patients are treated with prednisone or equivalent at a 1 mg/kg dose (Izzedine et al., 2014; Sales & Foresto, 2020). Immune-mediated toxicity may require temporary or permanent discontinuation of the offending agent.
- c) Patient and family education
  - (1) Educate patients and families regarding the risks of nephrotoxicity with the specific antineoplastic or cytotoxic regimens.
  - (2) Provide patients with a list of warning signs and symptoms that necessitate contacting their provider.
  - (3) Educate patients and families regarding the need for extraoral hydration while receiving nephrotoxic therapies.
  - (4) Provide patients with a list of drugs to avoid to decrease the risk of nephrotoxicity.

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## CHAPTER 20

# Altered Sexual and Reproductive Functioning

### A. Alterations in sexual functioning

#### 1. Overview

- a) Sexuality is both a high priority and an unmet need for patients undergoing cancer treatment and cancer survivors (Almont et al., 2017).
- b) Sexual dysfunction after cancer is frequently reported and is associated with poor quality of life among survivors (Sears et al., 2018).
- c) Sexuality, and therefore sexual toxicities, are a concern for individuals across the age spectrum.
  - (1) Most patients are concerned about sexuality despite their prognosis, and younger patients are more likely to experience persistently impaired sexuality following cancer treatment (Almont et al., 2017; Farthmann et al., 2016).
  - (2) Studies suggest that despite knowing about the impacts of cancer and its treatment on sexuality, patients are often not provided with adequate information and resources (Pitcher et al., 2020). This lack of education results in missed opportunities for sexual rehabilitation (Almont et al., 2017).
  - (3) Approximately 20% of men with treatment-related issues consult with a healthcare provider about sexuality. Healthcare providers tend to ask women about sexuality less frequently than men (Ben Charif et al., 2016; Schover, 2016).
- d) More research is needed on the effects of cancer and sexuality in the LGBTQ+ community (Schabath et al., 2019). Despite an estimated 100,000 cancer diagnoses annually within the LGBTQ+ community, limited efforts have been made to address sexual disparities in this population (Schabath et al., 2019).

#### 2. Pathophysiology

- a) Sexual dysfunction related to cancer and its treatment results from chemotherapy, surgery, and radiation therapy (Priviero & Webb, 2021). These

treatment modalities cause disruptions to blood vessels, nerves, and hormones that contribute to sexual dysfunction (Priviero & Webb, 2021). Women and men can experience different forms of sexual dysfunction.

##### (1) Women

- (a) Premature ovarian failure resulting in loss of ovarian androgen and precursor sex hormones (i.e., estrogen, progesterone, and testosterone) (N. Bennett et al., 2016)
- (b) Neurotoxic chemotherapy hypothesized to damage genital sensory neurons (Marchand & Bradford, 2017)
- (c) Estrogen deprivation resulting from hormone manipulation (N. Bennett et al., 2016)

##### (2) Men

- (a) Alterations in testosterone levels caused by disease or cancer treatments
- (b) Chemotherapy that may be neurotoxic to erectile nerves and affect penile blood supply, causing erectile problems (Voznesensky et al., 2016)
- (c) Erectile dysfunction is classified as a psychogenic, vasculogenic, neurogenic, endocrinologic, end-organ disease, or iatrogenic condition (McMahon, 2019).

##### i. Psychogenic

- Dysfunction may result from anxiety, fatigue, or depression that often manifests as a lack of interest in sexual activity or a decline in arousal ability.
- Anxiety may be related to a relationship, sexual performance, or depression.

##### ii. Vasculogenic

- Dysfunction is associated with alterations in penile blood flow or damage to the pudendal or penile arteries.
- Veno-occlusive dysfunction also may occur. It is caused by a failure of the passive venous outflow obstructive mechanism, resulting in the inability of sinusoids to trap blood.

### iii. Neurogenic

- Dysfunction is associated with any disease or dysfunction involving the brain, spinal cord, or cavernous and pudendal nerves.
- Causes can include pelvic surgery, spinal cord injury, and multiple sclerosis (McMahon, 2019).

### iv. Endocrinologic

- It is associated with hypogonadism and testosterone deficiencies.
- Testosterone is associated with all stages of physiologic development in males, including sexual development (Mirone & La Rocca, 2020).
- Testosterone production can be influenced by tumor growth or cancer treatment that contributes to hypogonadism.
- Treatment-related hyperprolactinemia may suppress the production of testosterone.
- Pure hormone-driven erectile dysfunction is rare.

(d) End-organ disease is associated with pelvic or genital radiation therapy and Peyronie disease (McMahon, 2019).

(e) Iatrogenic dysfunction is associated with side effects of certain medications, such as thiazide diuretics and selective serotonin reuptake inhibitor antidepressants (McMahon, 2019).

## 3. Incidence

a) General: Sexual dysfunction reporting in cancer survivors is 17%–100% (Priviero & Webb, 2021). Patients with cancer and survivors can experience sexual alterations regardless of cancer type.

These alterations are commonly related to cancer treatments (American Cancer Society, 2019). Up to 68% of childhood cancer survivors report sexual dysfunction (Priviero & Webb, 2021). The probability of sexual dysfunction increases over time for young adults (Acquati et al., 2018).

### b) Women

- (1) The incidence of sexual dysfunction is 35%–94% across female cancer survivors and often goes unaddressed (Falk & Dizon, 2020; Miller et al., 2019).
- (2) In women with gynecologic cancers, 40%–100% report sexual dysfunction after cancer treatment (Pitcher et al., 2020).
- (3) Among young adult breast cancer survivors, 52% report sexual dysfunction (Acquati et al., 2018).
- (4) A decrease in sexual desire and libido occurs in over half of women with ovarian or breast cancers (Whicker et al., 2017; Widiarti et al., 2019). Studies have shown that sexual desire is directly related to side effects of chemotherapy, as well as social support and body image (Widiarti et al., 2019).
- (5) Dyspareunia or pain during intercourse has been reported by women after various cancer diagnoses and treatment modalities (Duimering et al., 2020).
- (6) Vaginal stenosis is a known toxicity of radiation treatment in patients with endometrial and cervical cancers, with an average incidence of about 73% (Campitelli et al., 2018; de Moraes Siqueira et al., 2021).

### c) Men

- (1) Approximately 30.9% of men with cancer are dissatisfied with sexual functioning, whereas 18.2% of women with cancer are dissatisfied (Jackson et al., 2016).
- (2) Erectile dysfunction
  - (a) The incidence of cancer-related erectile dysfunction is 24%–87% (Madan et al., 2020).
  - (b) Erectile dysfunction is the most common sexual side effect for men receiving cancer treatment, but it is often underreported (Madan et al., 2020; Mayo Clinic, 2020a).
  - (c) Following radical prostatectomy, 79% of men reported erectile dysfunction two years after surgery and 72% five years after surgery (Madan et al., 2020). Approximately 9%–40% of men regain sexual function following a prostatectomy.



- (d) Following radiation therapy for prostate cancer, 60% of men reported erectile dysfunction two years after treatment and 72% five years after treatment (Madan et al., 2020).
  - (e) Long-term survivors (more than 15 years) reported erectile dysfunction consistent with their five-year follow-up (Madan et al., 2020).
  - (3) Reduced penile length is reported in men following prostatectomies and cystectomies (Madan et al., 2020).
  - (4) Approximately 11% of testicular cancer survivors report loss of desire, and 51% report ejaculation problems (Acquati et al., 2018).
4. Risk factors
- a) General (Falk & Dizon, 2020)
    - (1) Individuals with cancer and other chronic illness states, specifically uncontrolled hypertension, thyroid dysfunction, hyperlipidemia, anemia, fatigue, and depression, are at an increased risk for sexual dysfunction. Uncontrolled diabetes can also cause vascular dysfunction and decreased blood flow to the pelvic region, inhibiting engorgement and excitement.
      - (a) Diuretics and antihypertensive medications are associated with decreased libido and orgasm.
      - (b) Similarly, selective serotonin reuptake inhibitors and other antidepressants may inhibit sexual desire, arousal, and orgasm.
    - (2) A higher probability of reporting sexual dysfunction exists in patients who are female, older, married, treated with chemotherapy, and reported comorbid psychological distress and lower social support (Aquatic et al., 2018).
    - (3) Gender and sexual minorities are at a higher risk for cancer effects on sexual dysfunction due to a lack of knowledge and skill from providers (Kamen et al., 2018).
    - (4) Sexual dysfunction related to antineoplastic agents is common among cancer survivors treated as adults and adults treated as children (Priviero & Webb, 2021). The following agents are used in various combinations; thus, sexual side effects may be cumulative.
      - (a) Alkylating agents (e.g., busulfan, cyclophosphamide, ifosfamide, nitrogen mustard, platinum-based chemotherapies) cause nausea and vomiting, which can significantly decrease sexual desire (Falk & Dizon, 2020; Weitzner et al., 2019).
      - (b) Antimetabolites (e.g., cladribine, cytarabine, hydroxyurea, methotrexate) cause malaise, mucositis, nausea, and vomiting (Davis & Howard, 2019).
      - (c) Antitumor antibiotics (e.g., daunorubicin, doxorubicin, mitoxantrone) cause nausea, vomiting, and mucositis (Davis & Howard, 2019).
      - (d) Vinca alkaloids (e.g., vincristine, vinblastine, vinorelbine) cause peripheral neuropathy, which may affect sensation in the hands and fingers and decrease sexual desire (Davis & Howard, 2019).
      - (e) Most immunotherapy agents can cause fatigue, flu-like symptoms, and changes to body image (Abueg & Keith, 2019).
      - (f) Targeted therapy can cause fatigue, diarrhea, and rash with the potential to affect body image (Abueg & Keith, 2019).
  - b) Women
    - (1) Disease factors (Falk & Dizon, 2020)
      - (a) The risk of sexual dysfunction increases for women with rectal, gynecologic, or breast cancers, especially hormone-sensitive cancers (Mayo Clinic, 2020b).
      - (b) The risk for premature or permanent ovarian failure increases with age.
    - (2) Antineoplastic therapies
      - (a) Chemotherapy (Falk & Dizon, 2020; see Chapter 6)
        - i. Chemotherapy can cause hair loss, nausea and vomiting, diarrhea, or constipation, which may decrease sexual desire and frequency.
        - ii. Chemotherapy can cause direct toxicity to the pelvis and vagina.
      - (b) Hormone therapy (see Chapter 7)
        - i. Aromatase inhibitor risk to sexual health is higher than estrogen receptor modulators, causing vaginal dryness, atrophy, and dyspareunia (Sánchez-Rovira et al., 2020). Aromatase inhibitors are preferred for postmenopausal women

- with estrogen-sensitive cancers (Advani et al., 2017).
- ii. Estrogen receptor modulators, such as tamoxifen, can cause dyspareunia (painful intercourse) regardless of menopause status (Falk & Dizon, 2020).
- (c) Pelvic or anal irradiation contributes to ovarian failure (Falk & Dizon, 2020).
- (d) Bilateral oophorectomy (for cancer treatment or prevention) is equivalent to ovarian failure.
- (e) Gonadotropin-releasing agonists or antagonists for ovarian suppression can increase the risk of permanent ovarian failure (Falk & Dizon, 2020).
- (3) Systemic graft-versus-host disease can make vaginal intercourse impossible because of severe tissue damage to the vulva and vagina (Skorupska et al., 2019).
- (4) Subjectively, women report that fatigue, anxiety, depression, compromised self-esteem, general pain, appearance changes, and feelings of unattractiveness contribute to changes in sexual frequency and activities (Almont et al., 2017; Mollaioli et al., 2020; Widiанти et al., 2019).
- c) Men (Mayo Clinic, 2020a)
  - (1) Disease factors
    - (a) History of pelvic cancers (e.g., bladder, colorectal, prostate)
    - (b) Hypogonadism
  - (2) Antineoplastic therapies
    - (a) Surgery for bladder or rectal cancer
    - (b) Chemoradiation therapy for anal cancer
    - (c) Prostatectomy (both radical and nerve sparing)
    - (d) Damage to pelvic nerves
    - (e) Pelvic or total body irradiation
  - (3) Multimodal treatment (chemoradiation therapy) is more likely to cause sexual problems (Capogrosso et al., 2016).
  - (4) Subjectively, men report that erectile dysfunction, fatigue, pain, surgery, decreased body image, and aging were the primary causes of changes in sexual functioning (Mayo Clinic, 2020a).
- 5. Clinical manifestations
  - a) Sexual dysfunction is associated with fatigue, pain, nausea, incontinence, depression, and anxiety that can result in the discontinuation of sexual activity (McMahon, 2019).
  - b) Men and women report a decrease in sexual frequency and satisfaction following a cancer diagnosis and associated treatment (Olsson et al., 2018).
  - c) Women (Falk & Dizon, 2020)
    - (1) Most common manifestations
      - (a) Dyspareunia
      - (b) Vaginal dryness
      - (c) Decreased libido
    - (2) Effects may also include difficulty with sexual self-image, arousal, feeling pleasure, or achieving orgasm during sexual activity. Hair loss due to chemotherapy can contribute to negative body image, affecting sexual desire.
    - (3) Symptoms of chemotherapy-induced menopause are dramatic and may be worse for premenopausal women when diagnosed. Symptoms include the following (Farthmann et al., 2016; Valpey et al., 2019):
      - (a) Menstrual cycle changes with eventual cessation
      - (b) Hot flashes and insomnia
      - (c) Vaginal or vulvar dryness
      - (d) Dyspareunia
      - (e) Weight gain
      - (f) Mood changes and cognitive effects
  - d) Men (Madan et al., 2020)
    - (1) Most common manifestations are loss of libido and erectile dysfunction.
    - (2) Additional possible manifestations
      - (a) Perceived loss of genital length or penile shrinkage (Gentili et al., 2019)
      - (b) Changes in quality of and ability to achieve orgasm and pain associated with orgasm
      - (c) Feminization because of androgen deprivation (Gentili et al., 2019)
- 6. Collaborative management
  - a) A multimodal approach is needed to address all aspects of sexual dysfunction related to cancer treatment (Whicker et al., 2017).
    - (1) Screening for sexual dysfunction is essential for survivorship and patient quality of life (Falk & Dizon, 2020).
    - (2) Based on the individual, referrals may be needed to gynecology, urology, mental health, and internal medicine (Falk & Dizon, 2020).
    - (3) Sexual rehabilitation should be presented and offered to all patients with cancer.
    - (4) Quality of life restoration is an essential aspect of survivorship (Madan et al., 2020).
    - (5) Management of treatment-related sexual dysfunction should involve an interpro-

fessional approach consisting of medical and mental health components (Falk & Dizon, 2020).

- (6) This is important because sexual dysfunction emerges from physiologic changes related to cancer and its treatment and from the psychological sequelae of cancer, including negative body image and depression.

*b) General recommendations*

- (1) Address sexual health before cancer treatment rather than sexual dysfunction after it has progressed (Falk & Dizon, 2020).
- (2) Obtain a prior history of sexual experience, avoiding assumptions about sexual orientation and gender identity. Ask open-ended questions (Falk & Dizon, 2020).
- (3) Become knowledgeable about sexual orientation and gender identity before addressing the sexual needs of each patient (Schabath et al., 2019).
- (4) Focus on communication between patients and partners (Falk & Dizon, 2020).
- (5) Emphasize that sexual pleasure and intimacy can be found beyond penetrative intercourse (Falk & Dizon, 2020).
- (6) Identify coping mechanisms for the limitations of sex after cancer (Falk & Dizon, 2020).
- (7) Educate patients on the need for safe sex practices throughout cancer treatment (Frederick et al., 2020).
  - (a) Patients are usually advised to use a barrier (condom or dental dam) for penetrative intercourse and oral sex to protect their partner from exposure to metabolites of chemotherapy.
  - (b) Barrier protection should be used on the day of and for a week after chemotherapy administration.

*c) Women*

- (1) In addition to a physical examination, psychosocial assessment should focus on changes in spontaneous versus receptive sexual desire, barriers to sexual activity (e.g., pain), changes in relationship adjustment (if applicable), and assessment of risk factors (Marchand & Bradford, 2017). Validated instruments include the following:
  - (a) Female Sexual Function Index (Duijmering et al., 2020)
  - (b) Sexual Activity Questionnaire (Oppenheimer et al., 2019)

(c) Menopausal Sexual Interest Questionnaire (Advani et al., 2017)

(d) Patient-Reported Outcomes Measurement Information System Sexual Interest and Satisfaction Measure (PROMIS-SexFS) (Agochukwu et al., 2019)

- (2) Psychosocial counseling is recommended to improve desire, arousal, orgasm, intimacy in relationships, and body image. Couple-based interventions have demonstrated efficacy in improving sexual functioning (Barbera et al., 2017).
- (3) Distinct from psychosocial counseling, sex therapy may use a multimodal approach (e.g., education, communication, sensate focus, mindfulness) to enhance sexual desire (Marchand & Bradford, 2017).
- (4) Physical interventions
  - (a) Regular stimulation (e.g., masturbation) can also help to improve sexual response.
  - (b) Physical exercise or pelvic floor exercises can be helpful.
- (5) The first-line choice for managing menopausal symptoms should be nonhormone. Four nonhormone treatments appear to be beneficial for managing vasomotor symptoms (hot flashes) (Szabo et al., 2019).
  - (a) Gabapentin and pregabalin reduce vasomotor symptoms in breast cancer survivors.
  - (b) Selective serotonin reuptake inhibitors (e.g., citalopram, escitalopram, sertraline, fluoxetine, paroxetine) have been shown to reduce vasomotor symptoms in patients with breast cancer by 10%–40%. Tamoxifen competes for the same metabolic pathway as paroxetine and fluoxetine; therefore, those agents should not be used in women receiving tamoxifen therapy for breast cancer.
  - (c) Serotonin noradrenaline reuptake inhibitors, including venlafaxine and desvenlafaxine, have reduced vasomotor symptoms.
  - (d) Clonidine, an alpha-2 adrenergic agonist, is used as an antihypertensive medication and to treat vasomotor symptoms.
- (6) The decision to use hormone treatment in hormone-sensitive cancers should be carefully discussed with patients (Mayo Clinic, 2020b).

- (a) Local estrogen therapy for vaginal atrophy
      - i. Using low-dose estrogen can significantly decrease vulvo-vaginal dryness and associated pain (Falk & Dizon, 2020).
      - ii. Local estrogen use did not increase the risk of recurrence in women with hormone-sensitive breast cancer (Whicker et al., 2017).
      - iii. The safety of local estrogen for women on aromatase inhibitors is not yet established (Sulaica et al., 2016).
      - iv. Vaginal testosterone has proven efficacy in reducing vulvovaginal atrophy in women with breast cancer using aromatase inhibitors (Falk & Dizon, 2020).
    - (b) Systemic hormone replacement therapy has proven beneficial in ovarian and breast cancer survivors (Vermeulen et al., 2017).
  - (7) Other therapy agents are available, such as gels, creams, and suppositories (Barbera et al., 2017; Marchand & Bradford, 2017).
    - (a) Vaginal moisturizers can be used for daily comfort, and lubricants can be used during intercourse.
    - (b) Topical anesthetics may also be used to reduce pain during intercourse.
    - (c) Topical steroids, used to treat localized genital graft-versus-host disease, can help reduce symptoms (Jacobson et al., 2019).
  - (8) Vaginal dilators may be beneficial in the presence of vaginismus (involuntary muscle contraction) or vaginal stenosis, particularly among women who received radiation treatment for cervical cancer.
- d) Men
  - (1) Assessment should be conducted at each visit and include examining genital appearance, testing testosterone levels, and examining the prostate (Marchand & Bradford, 2017).
    - (a) The International Index of Erectile Function may be used to assess erectile dysfunction concerns quickly; however, it focuses on penile–vaginal intercourse and may not be appropriate to assess erectile dysfunction in men who have sex with men (Marchand & Bradford, 2017).
    - (b) The Patient-Reported Outcomes Measurement Information System (PROMIS) Sexual Interest and Satisfaction measures sexuality, sexual interest, satisfaction, and physical functionality in patients with prostate cancer (Agochukwu et al., 2019).
  - (2) Care coordination
    - (a) Coordinate interprofessional referrals, including urology and sex therapy.
    - (b) Begin penile rehabilitation early in the patient's treatment to improve erectile function (Yang et al., 2019).
    - (c) Psychosocial counseling is recommended to improve desire, arousal, orgasm, intimacy, and relationships (Barbera et al., 2017).
  - (3) Treatment options for erectile dysfunction
    - (a) Phosphodiesterase type 5 (PDE5) inhibitors, including sildenafil (Viagra®), tadalafil (Cialis®), and vardenafil (Levitra®), have demonstrated efficacy in supporting erectile function following nerve-sparing radical prostatectomy (Jo et al., 2018).
      - i. This drug class increases perfusion to the blood vessels of the corpus cavernosum of the penis by blocking the degradative action of cyclic granulocyte-macrophage inhibitor-specific PDE5 in smooth muscle cells.
      - ii. They are contraindicated with nitrates (Deng et al., 2017).
    - (b) Vacuum erection devices
      - i. Consists of a closed-ended, clear plastic cylinder and a vacuum that uses negative pressure to increase blood flow to the penis by distending the corporal sinusoids (Yang et al., 2019)
      - ii. Advantages
        - Easy to use, noninvasive, quick response with an average time to erection of two to three minutes; men have reported a reduction in penile shortening (Hecht & Hedges, 2016; Yang et al., 2019).

- Additionally, a fixed expense is associated with vacuum pumps (Hecht & Hedges, 2016).
  - iii. Disadvantages
    - Evidence-based guidelines are lacking, and the optimal level of negative pressure has not been appropriately established (Yang et al., 2019).
    - Men can experience pain and urethral constriction.
  - iv. Contraindicated with coagulation abnormalities and sickle cell disease
  - v. May be used in combination with PDE5 inhibitors (Falk & Dizon, 2020)
- (c) Prostaglandin E1 can be administered by suppository or intracavernosal injection to induce vasodilation and expansion of the corpora spongiosum to achieve an erection (Patel & Hsleh, 2016).
- i. It is typically used as second-line therapy in patients in whom PDE5 inhibitor therapy was unsuccessful or combined with other forms of penile rehabilitation (Patel & Hsleh, 2016).
  - ii. Intracavernosal injection is most effective when administered within three months of nerve-sparing radical prostatectomy.
  - iii. Suppositories may be used alone or with a vacuum erection device or PDE5 inhibitor. They have demonstrated increased efficacy when combined (Jo et al., 2018).
- (d) Penile prosthetic implants (Dadhich et al., 2017)
- i. Surgically implanted devices that may be noninflatable, semirigid, or inflatable, allowing for erection through manual manipulation or pump-facilitated inflation
  - ii. Advantages: Some studies suggest higher scores on measures of erectile function with implanted inflatable prosthetics than with medical management.
  - iii. Disadvantages: Invasive procedure; rare complications, including bladder injury, reservoir hernia, and reservoir erosion
  - iv. Minimally used, with less than 1% of patients reporting progression to prosthesis placement after cancer treatment
- (e) Other treatment modalities (Barbera et al., 2017)
- i. Venlafaxine, medroxyprogesterone acetate, cyproterone acetate, or gabapentin may be used to improve vasomotor symptoms.
  - ii. Some studies have suggested acupuncture may also be used to treat these symptoms.
- e) Assessment tools
- (1) Several models help communicate sexuality to patients. Historically, the most frequently used model is PLISSIT (permission, limited information, specific suggestion, intensive therapy) (Annon, 1976; M.R. Bennett, 2019). A more recent model specifically designed for the oncology population is BETTER (bring up, explain, tell, timing, educate, record) (Karakas & Aslan, 2019).
- (a) PLISSIT (M.R. Bennett, 2019)
- i. The first level involves giving the patients or clients permission to talk about sexual issues.
  - ii. The second level refers to the information given to patients in response to a question or observation.
  - iii. The third level involves making a specific suggestion to the patients or clients.
  - iv. The fourth level refers to the intensive therapy needed for severe or more long-standing sexual problems or referral to a specialist, such as a urologist or a gynecologist.
- (b) BETTER (Karakas & Aslan, 2019)
- i. The first level of intervention involves bringing up the topic.
  - ii. The second level involves explaining that sexuality is part of quality of life and that

patients can talk about this with the nurse.

- iii. Care providers should then tell patients that appropriate resources will be found to address their concerns.
- iv. Care providers should state that while the timing may not be appropriate now, patients can ask for information at any time.
- v. Patients should be educated about the sexual side effects of their treatment.
- vi. Finally, a note should be made in the patient's medical record stating that this topic has been discussed.

(c) Other assessment tools can be applied to assess sexual dysfunction, such as the 5 A's model, Changes in Sexual Functioning Questionnaire (CSFQ), and the Sexual Distress Scale-Revised (FSDS-R) (Duimering et al., 2020).

## 7. Patient and partner education

- a) Education and counseling should begin early to promote effective rehabilitation and limit sexual inactivity (Schover, 2016).
  - (1) Affected individuals should be encouraged to communicate openly about sex with their partners.
  - (2) Internet-based resources are recommended as self-help tools that individuals and their partners can use in the privacy of their homes.
  - (3) Patients and their partners should be encouraged to explore ways of expressing affection in the context of sexual dysfunction.
  - (4) Individuals or couples should be encouraged to view sexual activity as a chance to explore variety and fantasy rather than an action that needs to be performed correctly.
- b) Social support has a protective effect related to sexual dysfunction for young adults (Acquati et al., 2018); therefore, social connectivity should be emphasized and supported for young adults during and following cancer treatment.
- c) Access to support services can be challenging for gender and sexual minorities due to societal stigmas and biases, especially concerning services that have historically only served heterosexual patients (Kamen et al., 2018).

## B. Alterations in reproductive functioning

### 1. Overview

- a) Infertility, both temporary and permanent, is a possible side effect related to cancer type and any treatment received (Wettergren et al., 2020).
- b) Many young adult cancer survivors do not receive adequate information about treatment-related infertility and options for fertility preservation, which can lead to survivor regret (Chan et al., 2017; Fair et al., 2019).
- c) Attention to fertility concerns has been cited as an unmet need in 93% of adolescent and young adult survivors, and uncertainty about fertility status is common in young adult cancer survivors (Benedict et al., 2016; Wong et al., 2017).
- d) Attention to gender identity has also been identified as an unmet need in patients with cancer when addressing reproductive functioning, mainly due to provider knowledge regarding gender and sexual minorities (Kamen et al., 2018; Schabath et al., 2019).

### 2. Pathophysiology

- a) In women, chemotherapy causes damage to ovarian follicles, decreased ovarian volume, and decreased ovarian reserve.
- b) In men, gonadotropin and sperm production deficiencies (azoospermia) are common side effects of cancer treatment (Polackwich & Sabanegh, 2016).

### 3. Incidence

#### a) Women

- (1) Most female cancer survivors have reproductive alterations and distress (Wettergren et al., 2020).
- (2) Rates of chemotherapy-induced amenorrhea increase with age (Zavos & Valachis, 2016).
  - (a) Women younger than age 35: 26%
  - (b) Women aged 35–40 years: 39%
  - (c) Women older than age 40 years: 77%

#### b) Men

- (1) Infertility is dependent on the chemotherapy regimen, cumulative doses, and other therapies, such as radiation and surgical interventions (Vij & Gilligan, 2016).
- (2) Azoospermia rates range from 11%–100% (Ostrowski & Walsh, 2016).
- (3) Fertility-related distress in cancer survivors has not been well studied in men. Still, studies have shown that impaired infertility is directly related to decreased quality of life (Wettergren et al., 2020).

### 4. Risk factors

#### a) Disease-related risk factors



- (1) Women with ovarian cancer and hormone-sensitive breast cancer may have increased risk for infertility and genitourinary syndrome of menopause related to hypoestrogenism (Falk & Dizon, 2020).
  - (2) Men with testicular and Hodgkin lymphoma are more likely to have poor sperm quality prior to beginning treatment (Agarwal & Sharma, 2016).
- b) Treatment-related risk factors
- (1) Radiation therapy alone or in combination can significantly increase the risk of infertility (Clezki, 2016).
  - (2) High doses of alkylating agents pose the highest risk for infertility in pediatric cancer survivors and adult men and women (de Lambert et al., 2018).
    - (a) In women, procarbazine and the CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) regimen are associated with increased risk of infertility (Overbeek et al., 2017).
    - (b) In men, the most spermatotoxic chemotherapy drugs include nitrogen mustard derivatives (e.g., busulfan, melphalan) and alkylating agents (e.g., cyclophosphamide, procarbazine) (Vij & Gilligan, 2016).
      - i. Cyclophosphamide, ifosfamide, and procarbazine are gonadotoxic and associated with azoospermia (de Lambert et al., 2018; Moss et al., 2016).
      - ii. Antimetabolites can cause a temporary reduction in sperm count but are not known to cause infertility (Vij & Gilligan, 2016).
  - (3) Age
    - (a) Older age increases the risk for infertility in men and women.
    - (b) Chemotherapy accelerates reproductive aging in childhood cancer survivors (Anderson & Wallace, 2016).
5. Clinical manifestations
- a) Women (Campbell & Woodard, 2020)
- (1) Women with high levels of concern about fertility are more likely to experience depression.
  - (2) Women are also concerned about the effects of cancer treatment.
  - (3) Women who receive fertility preservation counseling experience improved quality of life and have better coping skills and less long-term regret.
- b) Men
- (1) Oligozoospermia occurs in approximately 50%–70% of men with cancer before treatment begins (Giwerzman, 2017; Polackwich & Sabanegh, 2016).
  - (2) Azoospermia occurs in 9.7%–21% of men at diagnosis (Ostrowski & Walsh, 2016).
    - (a) Recovery of spermatogenesis is typically observed within two to five years after chemotherapy, after which 8% of men remain azoospermic, with prolonged azoospermia occurring in up to 65% of individuals receiving greater than 600 mg/m<sup>2</sup> of cisplatin (Giwerzman, 2017).
    - (b) Among male survivors of childhood cancer, approximately 20% present with azoospermia, with an incidence of 15% in individuals treated with chemotherapy alone versus 33% among those treated with chemotherapy plus radiation (Giwerzman, 2017).
6. Collaborative management
- a) An interprofessional approach is needed to manage reproductive dysfunction properly.
- (1) Referrals to gynecology, urology, or internal medicine may be needed to address reproductive needs and quality of life (Falk & Dizon, 2020).
  - (2) Additionally, patients expressing distress related to potential or actual infertility may benefit from a referral to a psychologist (Falk & Dizon, 2020).
  - (3) Sexual rehabilitation should be presented and offered to all patients with cancer.
- b) Women (Pereira & Schattman, 2017)
- (1) Oocyte and embryo cryopreservation techniques are established methods. Ovarian stimulation followed by cryopreservation is the most reliable technique for fertility preservation.
  - (2) Ovarian stimulation usually requires two weeks of gonadotropin injections.
  - (3) Ovarian stimulation with subsequent cryopreservation has proven to be efficacious and safe for patients with cancer.
  - (4) In recent years, ovarian cortex or immature oocyte cryopreservation has become an alternative for patients (de Lambert et al., 2018).
  - (5) Controversy exists about using gonadotropin-releasing hormone analogs to protect the ovaries from damage. This controversy is due to initial observations in which data might have been misinter-



- preted and studies provided contradicting results (Oktay & Bedoschi, 2016).
- (6) Ovarian suppression is not likely to benefit despite support for this strategy and apparent safety (Demeestere et al., 2016; Hickman et al., 2016; Kim et al., 2016).
  - (7) The return of menstrual periods does not necessarily indicate good ovarian function, and, in turn, lack of menstruation does not mean that ovarian function has ceased.
- c) Men
- (1) Sperm cryopreservation before treatment is highly effective, as sperm remain viable after freezing and can be used to fertilize ovum.
  - (2) Semen samples should be collected 48–72 hours apart (Agarwal & Sharma, 2016).
  - (3) Electroejaculation can be used in prepubertal males who are embarrassed or unable to produce a semen sample. This requires general anesthesia but can be done at the time of another surgical procedure, such as bone marrow aspiration (Romao & Lorenzo, 2017).
  - (4) Cryopreservation of testicular tissue is an experimental procedure that may offer hope to prepubertal boys (Wise, 2016).
7. Patient and family education (Hershberger et al., 2016)
- a) Decisions about fertility treatments must be made when patients are trying to cope with a cancer diagnosis; priorities may change over time, and some decisions are made without proper knowledge.
    - (1) It is essential to educate patients honestly and directly, as they may assume that modern reproductive technologies will result in a future pregnancy.
    - (2) A strong desire to be a biologic parent motivates some patients to attempt to preserve fertility.
  - b) Patients and caregivers need to be educated on possible barriers to fertility preservation (Flink et al., 2017).
    - (1) Urgency to initiate cancer treatment and limited time to complete fertility preservation
    - (2) Inadequate information on fertility preservation options from providers. The need for a referral to an oncofertility specialist may exist, which may not be available to patients.
    - (3) Cost associated with fertility preservation
    - (4) Sociodemographic factors (e.g., age, race, relationship status)
  - c) Parents of a child with cancer must make decisions about treatment for their child and may not be ready to discuss sperm banking or ovarian preservation with their child or healthcare providers, as their priority is to save their child's life (Wong et al., 2017).
  - d) Access to fertility services
    - (1) An interprofessional approach is optimal to address the complex ethical and psychological issues. Nurses who have longitudinal relationships with patients are vital to ensuring that information is provided to patients (Quinn et al., 2016).
    - (2) Barriers to fertility services
      - (a) Access to fertility services is related to a patient's developmental stage, age, literacy level, cultural beliefs, sexual orientation, gender identity, and assumptions made by clinicians (Ghazeeri & Khalife, 2020; Schabath et al., 2019). Demographic disparities and the availability of resources also impact access to fertility preservation (Flink et al., 2017).
      - (b) Age-appropriate information and services are an unmet need for adolescents and young adults with cancer, as is fertility-related follow-up after the completion of treatment (Bibby et al., 2017).
      - (c) Referrals for sperm banking remain low—29% of young men reported receiving counseling, and 11% attempted sperm banking (Grover et al., 2016).
      - (d) Only 34%–72% of women report receiving fertility preservation counseling and information (Campbell & Woodard, 2020).
      - (e) Patients who are not adequately educated on fertility preservation before beginning cancer treatment can make uninformed decisions that may permanently impact fertility and have lifelong consequences (Giles, 2017).
  - e) General education (Kelvin, 2020)
    - (1) Address the risk of infertility and discuss fertility preservation options with patients as part of informed consent before cancer therapy. Sperm and embryo cryopreservation are well established as the standard of care.

- (2) Encourage patients to participate in registries and clinical trials related to fertility preservation.
- (3) Provide information about the timeline for fertility preservation and how it may affect treatment and overall outcomes.
- (4) Advise patients of the potential toxicity to reproductive material or the loss of opportunity to preserve reproductive material after the start of chemotherapy.
- (5) Engage patients, partners, and caregivers (if applicable) in discussions of cryopreservation options.

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## CHAPTER 21

# Cutaneous Toxicities and Alopecia

### A. Cutaneous toxicity

#### 1. Overview

- a) For years, the cutaneous side effects from conventional cytotoxic chemotherapy agents have been observed and described in detail.
- b) With the introduction of targeted therapies and immunotherapies, cutaneous toxicities have increased.
- c) Cutaneous toxicities can result in treatment interruptions and have financial implications and psychosocial impacts.
- d) As the number of agents and uses for targeted therapy and immunotherapy increase, so does the need to recognize and treat the dermatologic side effects of these agents (Lacouture et al., 2021).
- e) See Table 21-1 for cutaneous reactions and management of toxicities from chemotherapy, targeted therapy, and immunotherapy agents.

#### 2. Pathophysiology, incidence, risk factors, and clinical manifestations

##### a) Chemotherapy

- (1) Numerous cutaneous side effects have been reported from traditional chemotherapy drugs, including cytarabine, anthracyclines (e.g., doxorubicin), 5-fluorouracil (5-FU), capecitabine (5-FU prodrug), taxanes (e.g., docetaxel), and methotrexate.

(a) Reports include clinical and histologic findings that have significant overlap. Cutaneous adverse events from chemotherapy can affect the skin, hair, nails, and mucosa.

(b) Cutaneous side effects from chemotherapy occur due to disruptions in the cell cycle phases. The specific phase in which the disruption occurs will cause a specific type of cutaneous reaction (Reyes-Habito & Roh, 2014a).

- i. Alkylating agents, such as cyclophosphamide, cause dam-

age in all phases of the cell cycle and tend to cause hyperpigmentation.

- ii. Antimetabolites, such as gemcitabine, damage cells in the S phase and cause cutaneous effects, such as maculopapular rash, hand-foot syndrome, and hyperpigmentation.
- iii. Antitumor antibiotic agents, such as doxorubicin, cause damage in all phases of the cell cycle and lead to reactions, such as hand-foot syndrome and follicular rash.
- iv. Mitotic inhibitors, including taxanes, cause damage in the M phase of the cell cycle. Cutaneous reactions from these agents include hand-foot syndrome, nail changes, and erythema multiforme.
- v. Topoisomerase inhibitors, such as topotecan and etoposide, affect the cell cycle during the S or G<sub>2</sub> phase. Cutaneous reactions seen with these agents include hand-foot syndrome and paronychia (Reyes-Habito & Roh, 2014a).

- (2) Hand-foot syndrome (palmar-plantar erythroderma) occurs in 6%–62% of patients receiving single-agent therapy, increasing to as high as 89% in those receiving multiple agents.

(a) Development of hand-foot syndrome is usually seen within days to weeks after initiation of therapy.

(b) Presenting symptoms include numbness, paresthesia and erythema, or hyperpigmentation in patients with

**TABLE 21-1.** Cutaneous Reactions to Antineoplastic Agents

| Cutaneous Reaction                         | General Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Chemotherapy                                                                                                                                                                                                                                         | Targeted Therapy                                                                                                       | Immunotherapy                      |
|--------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|------------------------------------|
| Acneiform eruptions or papulopustular rash | <p>EGFRI-mediated rashes generally follow a well-characterized clinical course. Within the first week of treatment, patients experience sensory disturbance with erythema and edema; from weeks 1–3, the papulopustular eruption manifests, followed by crusting at week 4. Despite successful treatment, erythema and dry skin may persist in the areas previously affected by skin rash through weeks 4–6.</p> <p>It generally presents as diffuse erythema over the face and body, progressing to follicular papules and pustules resembling acne.</p> <p>Causative chemotherapy agents should be discontinued. Causative EGFRIs may not need to be discontinued.</p> <p>The disorder is characterized by an eruption consisting of papules (small raised pimples) and pustules (small pus-filled blisters), typically appearing on the face, scalp, and upper chest and back. Unlike acne, this rash does not present with whiteheads or blackheads and can be symptomatic, with itchy or tender lesions.</p> <p>See text for grading and management of papulopustular rash.</p> | –                                                                                                                                                                                                                                                    | Brigatinib, dabrafenib, dacomitinib, erlotinib, everolimus, gefitinib, lapatinib, temsirolimus, trametinib, vandetanib | Cetuximab, durvalumab, panitumumab |
| Acral erythema                             | <p>Acral erythema consists of erythema, swelling, and pain of the digits. It usually occurs 1–14 days after treatment starts and lasts for 1–2 weeks.</p> <p>It generally presents as dysesthesia (altered sensation of the skin) with tingling in the hands and feet progressing to pain.</p> <p>After 4–5 days of intense edematous erythema and even fissures of the palms, soles, and digital joints, progression to desquamation and reepithelialization occurs. It resolves 5–7 days after therapy is discontinued. The etiology is not clear but may be related to drug concentration in eccrine glands of the palms and soles.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                           | Amsacrine, bleomycin, capecitabine, cyclophosphamide, cytarabine, etoposide, docetaxel, doxorubicin, 5-FU, floxuridine, gemcitabine, hydroxyurea, liposomal doxorubicin, mercaptopurine, methotrexate, mitotane, paclitaxel, teniposide, vinblastine | Axitinib, dasatinib, everolimus, sorafenib, sunitinib                                                                  | –                                  |

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**TABLE 21-1.** Cutaneous Reactions to Antineoplastic Agents (*Continued*)

| Cutaneous Reaction                 | General Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Chemotherapy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Targeted Therapy                                          | Immunotherapy                              |
|------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|--------------------------------------------|
| Acral erythema<br>( <i>Cont.</i> ) | Applying cold compresses and elevating the hands and feet during drug administration may minimize the incidence and degree of toxicity.<br>Skin care and comfort measures are instituted as soon as symptoms are evident. Supportive care may include wound dressings, analgesia (pain relief), and cold compresses.                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                           |                                            |
| Beau lines                         | Beau lines are transverse ridges across the nail plate. These findings are benign, dose related, and resolve with cessation of chemotherapy.                                                                                                                                                                                                                                                                                                                                                                                                                                   | Bleomycin, cisplatin, docetaxel (taxanes), doxorubicin, melphalan, vincristine; capecitabine, hydroxyurea                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Beau lines and nail changes are common with EGFRIs.       | –                                          |
| Dystrophy                          | Dystrophy is a transverse midline linear groove in the nail plate.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Bleomycin, hydroxyurea                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Dystrophy and nail changes are common with EGFRIs.        | –                                          |
| Erythema multiforme                | The condition generally presents as a maculopapular erythematous lesion that may progress to vesicles and also can progress to Stevens-Johnson syndrome and toxic epidermal necrolysis.<br>Record description, presentation, and severity (use a grading scale). Consult with a physician regarding possible etiology. Consider discontinuing the offending chemotherapy agent. Causative EGFRIs may not need to be discontinued.<br>Examine areas of tissue breakdown, and attend to comfort measures with skin care and pain management strategies (see guidelines in text). | The condition is infrequently associated with chemotherapy. High-dose combination chemotherapy produces the highest risk. It is characterized by lesions over the extremities and often involving mucous membranes. Bleomycin, busulfan, cytarabine, etoposide, hydroxyurea, methotrexate, and procarbazine are associated with these lesions, which sometimes progress to generalized blistering.<br>Amifostine, cladribine, cyclophosphamide, daunorubicin, doxorubicin, docetaxel, 5-FU, ifosfamide, mechlorethamine, mitomycin C, mitotane, paclitaxel, vinblastine<br>Hormone therapy: tamoxifen | Alpelisib, apalutamide, duvelisib, gefitinib, vemurafenib | Bexarotene, durvalumab, enfortumab vedotin |

(Continued on next page)

**TABLE 21-1.** Cutaneous Reactions to Antineoplastic Agents (*Continued*)

| Cutaneous Reaction                                | General Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Chemotherapy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Targeted Therapy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Immunotherapy                                                                                                                                              |
|---------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Hair changes: alopecia, hirsutism, hypertrichosis | <p>Several chemotherapy drugs can cause hair changes and hair loss. Dose, route of administration, the combination of drugs, and other individual characteristics will influence the occurrence and degree of hair loss.</p> <p>Hair changes may occur 2–3 months after initiation of EGFR therapy, with hair thinning and developing a dry, brittle, or curly texture.</p> <p>Hirsutism is characterized by excess hair growth in women in anatomic sites where growth is typically a male characteristic (e.g., beard, mustache, hair on chest and abdomen).</p> <p>Hypertrichosis is characterized by hair density or length beyond the accepted limits of normal in a particular body region or a particular age or race.</p>                                                                                                                                                                                                            | <p>Hair changes: bexarotene, carboplatin, cisplatin, cyclophosphamide, dactinomycin, doxorubicin, etoposide, hexamethylmelamine, ifosfamide, paclitaxel, vincristine</p> <p>Alopecia: bleomycin, carboplatin, cisplatin, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, docetaxel, doxorubicin, epirubicin, eribulin, etoposide, 5-FU, hydroxyurea, ifosfamide, ixabepilone, methotrexate, paclitaxel</p>                                                                                                                 | <p>Alopecia: abemaciclib, alpelisib, axitinib, dabrafenib, dacomitinib, dasatinib, encorafenib, erdafitinib, eribulin, erlotinib, gefitinib, lapatinib, lenvatinib, nilotinib, pazopanib, pemigatinib, ribociclib, ripretinib, sorafenib, talazoparib tosylate, tazemetostat, vemurafenib, vismodegib</p> <p>Alopecia, hirsutism, and hypertrichosis: everolimus</p> <p>Hair color changes and alopecia: avapritinib, cabozantinib, pazopanib, sunitinib, tipiracil, trifluridine</p> <p>Hair color changes: imatinib, pexidartinib, selumetinib</p> | <p>Brentuximab, cetuximab, enfortumab vedotin, margetuximab-cmkb, mogamulizumab, panitumumab, pegylated IFN alfa-2b, sacituzumab</p> <p>govitecan-hziy</p> |
| Hyperpigmentation                                 | <p>Hyperpigmentation is the darkening of an area of skin or nails caused by increased melanin.</p> <p>Cutaneous hyperpigmentation associated with chemotherapy can present in localized or generalized patterns affecting the skin, teeth, or nails.</p> <p>Patients should avoid sun exposure or use effective sun barrier preparations to minimize the risk of hyperpigmentation. Sun exposure aggravates hyperpigmentation. It occurs most commonly in people of Mediterranean descent.</p> <p>Darkening may occur within 2–3 weeks of chemotherapy or immunotherapy and persist for months following the completion of therapy.</p> <p>Postinflammatory hyperpigmentation is seen following acneiform eruption or other causes of skin inflammation, such as eczema or an inflamed sebaceous cyst.</p> <p>No treatment or prevention methods exist, but these changes will usually resolve within months after cessation of therapy.</p> | <p>Bleomycin, busulfan, capecitabine, carboplatin, cisplatin, cyclophosphamide, dacarbazine, dactinomycin, daunorubicin, docetaxel, doxorubicin, etoposide, 5-FU, hydroxyurea, idarubicin, ifosfamide, melphalan, methotrexate, mitomycin C, mitoxantrone, nitrogen mustard, nitrosoureas, oxaliplatin, paclitaxel, prednisolone, 6-mercaptopurine, thiopeta, vincristine</p> <p>Flagellate streaks of hyperpigmentation caused by nails scratching the skin have been reported with parenteral and intrapleural administration of bleomycin.</p> | <p>Gilteritinib, imatinib, sunitinib</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | –                                                                                                                                                          |

(Continued on next page)

**TABLE 21-1.** Cutaneous Reactions to Antineoplastic Agents (*Continued*)

| Cutaneous Reaction          | General Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Chemotherapy                                                                                                                                                                                                         | Targeted Therapy                                                                                             | Immunotherapy          |
|-----------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|------------------------|
| Nail changes                | –                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Cyclophosphamide, daunorubicin, docetaxel, doxorubicin, ifosfamide                                                                                                                                                   | Bevacizumab, dacomitinib, erdafitinib, gefitinib, neratinib, osimertinib, sorafenib, sunitinib, temsirolimus | Cetuximab, panitumumab |
| Nail shedding (onycholysis) | Loss of all or a portion of the nail                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Bleomycin, capecitabine, cisplatin, cyclophosphamide, docetaxel, doxorubicin, etoposide, hydroxyurea, ixabepilone, melphalan, mitoxantrone, topical 5-FU, vinblastine, vincristine, weekly paclitaxel administration | Dacomitinib, erdafitinib, everolimus, neratinib, pemigatinib                                                 | –                      |
| Painful fissures            | <p>Skin fissures and deep cracks in the skin can form due to significant xerosis and often occur in the fingertips, palms or knuckles, and soles. Fissures are a late side effect of EGFRi therapy, occurring around 30–60 days into therapy. They can be very painful and create a risk for infection.</p> <p>Cyanoacrylate glue (liquid bandage formulations) may help protect the fissures. Treat topically with propylene glycol 50% in water for 30 minutes under plastic occlusion every night, followed by applying hydrocolloid dressing, antiseptic baths, or topical application of silver nitrate.</p> <p>For painful fissures on toes, use protective footwear and a topical corticosteroid, thick moisturizer, or barrier cream (e.g., petroleum jelly, zinc oxide).</p> | –                                                                                                                                                                                                                    | EGFRi therapy can lead to painful fissures.                                                                  | Panitumumab            |

(Continued on next page)

**TABLE 21-1.** Cutaneous Reactions to Antineoplastic Agents (*Continued*)

| Cutaneous Reaction                                     | General Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Chemotherapy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Targeted Therapy                                                                                                                                                                                                                                                                                                 | Immunotherapy                                |
|--------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|
| Palmar-plantar erythrodysesthesia (hand-foot syndrome) | <p>It first appears as mild redness on the palms and soles with tingling sensations in the hands, usually at the fingertips; symptoms progress to a more intense burning pain and tenderness.</p> <p>Palms and soles appear edematous, and patients may have difficulty walking or grasping objects.</p> <p>Ulceration may occur if therapy is not halted.</p> <p>Incidence and severity of symptoms are related to protracted exposure of cells to the drug. Symptoms usually develop 2–12 days after the administration of chemotherapy. Early recognition and cessation of drug administration are critical to symptom management.</p> <p>Symptoms may include flaking, swelling, small blisters, or small sores.</p> <p>Prevention and treatment include reducing exposure of hands and feet to friction and heat by having patients avoid hot water (e.g., washing dishes, long showers, hot baths), impact on their feet (e.g., jogging, aerobics, walking, jumping), use of tools that require them to squeeze their hand on a hard surface (e.g., garden tools, household tools, kitchen knives), and rubbing (e.g., applying lotion, massaging).</p> <p>Dose reduction may minimize the risk of recurrence.</p> | <p>Bleomycin, capecitabine, cisplatin, cyclophosphamide, cytarabine, daunorubicin, docetaxel, doxorubicin, etoposide, 5-FU (given in prolonged infusion), floxuridine, fludarabine, gemcitabine, hydroxyurea, idarubicin, ixabepilone, liposomal encapsulated doxorubicin, methotrexate, mitotane, thiotepa, vinorelbine</p> <p>Incidence is 50% (although reports vary) in patients receiving liposomal encapsulated doxorubicin. Incidence correlates with higher doses and an increased number of cycles.</p> <p>Combination therapy</p> <ul style="list-style-type: none"> <li>• Docetaxel and capecitabine (56%–63%)</li> <li>• Doxorubicin and continuous 5-FU (89%)</li> </ul> | <p>Hand-foot skin reaction is common with multikinase inhibitors and develops within the first 1–4 weeks of treatment.</p> <p>Axitinib, dacoritinib, erdafitinib, everolimus, gilteritinib, lapatinib, lenvatinib, pazopanib, pemigatinib, ripretinib, sorafenib, rucaparib, sunitinib, tivozanib, tucatinib</p> | <p>Enfortumab vedotin, margetuximab-cmkb</p> |

(Continued on next page)

**TABLE 21-1.** Cutaneous Reactions to Antineoplastic Agents (*Continued*)

| Cutaneous Reaction | General Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Chemotherapy                                                                   | Targeted Therapy                                                                                                                                                                                                                                                                                                                                                   | Immunotherapy                       |
|--------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|
| Paronychia         | <p>Paronychia is characterized by tender, edematous, and often purulent nail fold inflammation. Fingernails and toenails may be affected, with the first digits the most commonly affected.</p> <p>It often is delayed, developing 4–8 weeks after the start of therapy and occurring in 10%–15% of patients.</p> <p>Encourage preventive measures, such as keeping hands dry and out of the water if possible, wearing gloves while cleaning (e.g., household, dishes), avoiding friction and pressure on the nail fold or manipulating the nail, and wearing comfortable shoes.</p> <p>Treatment includes topical steroids with antiseptic soaks to prevent infections.</p> | Bleomycin, cyclophosphamide, docetaxel, doxorubicin, hydroxyurea, methotrexate | Afatinib, dacomitinib, erlotinib, gefitinib, lapatinib, neratinib, pemigatinib, selumitinib                                                                                                                                                                                                                                                                        | Cetuximab, necitumumab, panitumumab |
| Photosensitivity   | <p>Photosensitivity presents as sunburn occurring after minimal sun exposure. It is an erythematous response to UV radiation; skin appears red with erythema, edema, and possibly vesicles.</p> <p>Patients are instructed to wear protective clothing and a hat when in the sun; avoid direct sunlight when possible, especially during peak hours between 10 am and 3 pm; and avoid tanning beds. They should wear a sunscreen with an SPF higher than 15.</p> <p>In addition to measures taken to avoid sun exposure, patients treated with EGFRIs are advised to wear sunscreen with an SPF of 30 or higher.</p>                                                          | Dacarbazine, 5-FU, high-dose methotrexate, vinblastine                         | <p>Patients treated with EGFRIs may develop photosensitivity characterized by erythema from UV-induced damage. Erythema may be painful and associated with desquamation. In severe cases, photosensitivity and erythema may be disabling or life threatening.</p> <p>Dabrafenib, dasatinib, imatinib, nilotinib, rucaparib, tivozanib, vandetanib, vemurafenib</p> | Cetuximab, panitumumab, tretinoin   |

(Continued on next page)

**TABLE 21-1.** Cutaneous Reactions to Antineoplastic Agents (*Continued*)

| Cutaneous Reaction  | General Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Chemotherapy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Targeted Therapy                                                                                                                                                                                                                                                                                                                                                                                  | Immunotherapy                                                                                                                                                                                                                                        |
|---------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Pruritus or itching | <p>Pruritus may be localized or generalized; symptoms may worsen with dehydration. Encourage patients to drink 8–10 glasses of fluid per day and minimize salt and alcohol intake.</p> <p>Recommended skin care includes medicated baths, anesthetic creams, and emollient creams. Mild soap designed for sensitive skin should be used, and perfumes, deodorants, cosmetics, and starch-based powders should be avoided. Instead of scratching, massaging, applying pressure, or rubbing with a soft cloth should be suggested.</p> <p>Wearing loose-fitting clothing and clothing made of cotton or other soft fabrics can alleviate pruritus. Use antibiotics if pruritus is secondary to infection. Use oral antihistamines, with increased doses at bedtime. Sedatives, tranquilizers, and antidepressants may be useful treatments. Aspirin seems to reduce itching in some patients but increases it for others. Aspirin combined with cimetidine may be effective for patients with Hodgkin lymphoma or polycythemia vera. Distraction, relaxation, positive imagery, or cutaneous stimulation are encouraged. A cool, humid environment may prevent skin from itching.</p> <p>Skin moisturizers and urea- or polidocanol-containing lotions are suitable to soothe pruritus. Systemic treatment with oral H<sub>1</sub>-antihistamines such as cetirizine, fexofenadine, or loratadine, and clemastine may provide relief of itching for patients with grade 2–3 pruritus.</p> | <p>Alkylating agents, antimetabolites, antibiotics, plant alkaloids, and nitrosoureas can cause pruritus. Agents most associated with hypersensitivities include cisplatin, cytarabine, daunorubicin, doxorubicin, L-asparaginase, and paclitaxel.</p> <p>L-asparaginase, carboplatin, cisplatin, cytarabine, daunorubicin, doxorubicin, etoposide, melphalan, pomalidomide, and teniposide can all cause a rash.</p> <p>Actinic keratoses: Topical 5-FU, cisplatin, cytarabine, dacarbazine, dactinomycin, docetaxel, doxorubicin, pentostatin, 6-thioguanine, vincristine</p> <p>Bendamustine, pralatrexate</p> | <p>Abemaciclib, alpelisib, afatinib, apalutamide, axitinib, bevacizumab, dacomitinib, dasatinib, encorafenib, entrectinib, erlotinib, gefitinib, glasdegib, imatinib, ivosidenib, lapatinib, neratinib, nilotinib, pexidartinib, osimertinib, ribociclib, rucaparib, selumetinib, sorafenib, sunitinib, tazemetostat, temsirolimus, tivozanib, trametinib, tucatinib, vandetanib, vemurafenib</p> | <p>Atezolizumab, avelumab, brentuximab, cemiplimab, cetuximab, enfortumab vedotin, IFN alfa-2a, IFN alfa-2b, ipilimumab, necitumumab, nivolumab, panitumumab, pegylated IFN alfa-2b, pembrolizumab, sacituzumab govitecan-hziy, tagraxofusp-erzs</p> |

(Continued on next page)

**TABLE 21-1.** Cutaneous Reactions to Antineoplastic Agents (*Continued*)

| Cutaneous Reaction               | General Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Chemotherapy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Targeted Therapy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Immunotherapy                                                                                                                                                                                                                                                                                                                 |
|----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Rash                             | <p>Manifestation of monoclonal antibody–induced skin rash: Rash appears to be dose related and generally evolves within 2–3 weeks of the start of treatment.</p> <p>Tyrosine kinase inhibitors can cause a dose-dependent maculopapular rash that usually affects the trunk and forearms.</p>                                                                                                                                                                                                                                                                                        | <p>L-asparaginase, bendamustine, carboplatin, cladribine, cyclophosphamide, cytarabine, dacarbazine, docetaxel, 5-FU, fludauridine, gemcitabine, hydroxyurea, ifosfamide, lomustine, methotrexate, paclitaxel, pemetrexed, pomalidomide, pralatrexate, vinblastine, vincristine</p> <p>Cytarabine can cause skin peeling.</p>                                                                                                                                                                                                                                                                 | <p>Abemaciclib, alpelisib, afatinib, apalutamide, avapritinib, axitinib, bevacizumab, bimimetinib, bortezomib, brigatinib, crizotinib, dabrafenib, dacomitinib, darolutamide, dasatinib, duvelisib, eltrombopag, encorafenib, entrectinib, erlotinib, everolimus, gefitinib, gilteritinib, glasdegib, imatinib, ivosidenib, lapatinib, lenvatinib, lorlatinib, neratinib, nilotinib, niraparib, pazopanib, pexidartinib, ribociclib, romidepsin, rucaparib, sorafenib, selpercatinib, selumetinib, sunitinib, tazemetostat, tivozanib, trametinib, tucatinib, umbralisib, vandetanib, vemurafenib, zanubrutinib</p> | <p>Atezolizumab, avelumab, blinatumomab, brentuximab, cemiplimab, cetuximab, denosumab, durvalumab, enfortumab vedotin, ipilimumab, lenalidomide, mogamulizumab, necitumumab, nivolumab, ofatumumab, panitumumab, pegylated IFN alfa-2b, pembrolizumab, pertuzumab, ramucirumab, sacituzumab, govitecan-hziy, trastuzumab</p> |
| Skin blistering                  | –                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 5-FU, vinblastine                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | –                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | IL-2                                                                                                                                                                                                                                                                                                                          |
| Skin depigmentation and vitiligo | Pigment changes occur due to inhibition of c-KIT, which is the protein that regulates melanocytes. Changes may be localized, patchy, or diffuse. They occur more often in darker skin. Effects can be reversed with dose reduction or discontinuation.                                                                                                                                                                                                                                                                                                                               | –                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Dasatinib, imatinib, nilotinib, pazopanib                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | –                                                                                                                                                                                                                                                                                                                             |
| Stevens-Johnson syndrome         | <p>Stevens-Johnson syndrome (also known as erythema multiforme major) is a rare, serious disorder in which the skin and mucous membranes react severely to a medication or infection. It often begins with flu-like symptoms, followed by a painful red or purplish rash that spreads and blisters, eventually causing the top layer of the skin to die and shed.</p> <p>Stevens-Johnson syndrome presents a medical emergency that usually requires hospitalization. Treatment focuses on eliminating the underlying cause, controlling symptoms, and minimizing complications.</p> | <p>Cases of Stevens-Johnson syndrome and toxic epidermal necrolysis, some fatal, have been reported when bendamustine was administered concomitantly with allopurinol and other medications known to cause these syndromes. The relationship with bendamustine cannot be determined.</p> <p>Stevens-Johnson syndrome has been reported with amifostine, L-asparaginase, bleomycin, capecitabine, chlorambucil, cladribine, cyclophosphamide, cytarabine, docetaxel, doxorubicin, etoposide, 5-FU, imatinib, methotrexate, paclitaxel, and procarbazine.</p> <p>Hormone therapy: letrozole</p> | <p>Alpelisib, bortezomib, cetuximab, duvelisib, gefitinib</p> <p>Sunitinib: If signs or symptoms are present, discontinue treatment and do not restart.</p> <p>Vemurafenib: Stevens-Johnson syndrome has been observed. Discontinue the drug permanently.</p>                                                                                                                                                                                                                                                                                                                                                       | <p>Atezolizumab, cetuximab, durvalumab, ipilimumab, lenalidomide, levamisole, mogamulizumab, rituximab, thalidomide</p>                                                                                                                                                                                                       |

(Continued on next page)



**TABLE 21-1.** Cutaneous Reactions to Antineoplastic Agents (*Continued*)

| Cutaneous Reaction         | General Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Chemotherapy                                                                                                                                                                                                                                                                                                                                                                                                                                     | Targeted Therapy                                                                                                                | Immunotherapy                                                                                  |
|----------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| Telangiectasia             | <p>The disorder is characterized by local dilation of small vessels, resulting in red discoloration of the skin or mucous membranes.</p> <p>During the development of acneiform eruption or subsequent flares of the rash, scattered telangiectasia may appear on the face, on and behind the ears, and on the chest, back, and limbs, usually in the vicinity of a follicular pustule. Unlike other telangiectasias, the lesions tend to fade over months, usually leaving some hyperpigmentation.</p> <p>Telangiectasia caused by treatment with EGFRIs, unlike spontaneous telangiectasia, will gradually disappear over months. In select cases, electrocoagulation or pulsed dye laser therapy can be applied to accelerate disappearance.</p> <p>Radiation may cause telangiectasia, which is thought to be related to the destruction of the capillary bed. It generally is considered a permanent change in the vessel.</p> | Topical carmustine and mechlorethamine (nitrogen mustard) cause vessel fragility and destruction.                                                                                                                                                                                                                                                                                                                                                | Scattered telangiectasia can be seen with the development of any acneiform eruption caused by EGFRIs.                           | –                                                                                              |
| Toxic epidermal necrolysis | <p>Toxic epidermal necrolysis is most commonly drug induced. However, the disorder has other potential etiologies, including infection, malignancy, and vaccinations. Toxic epidermal necrolysis is idiosyncratic, and its occurrence is not easily predicted.</p> <p>Some authors believe that Stevens-Johnson syndrome is a manifestation of the same process involved in toxic epidermal necrolysis, with the latter involving more extensive necrotic epidermal detachment. Toxic epidermal necrolysis involves &gt; 30% of the body surface, whereas Stevens-Johnson syndrome involves &lt; 10%.</p> <p>It may be difficult to distinguish from grade 4 acute GVHD of the skin.</p>                                                                                                                                                                                                                                            | <p>Bendamustine: In combination with rituximab, one case of toxic epidermal necrolysis occurred. Toxic epidermal necrolysis has been reported with rituximab. Report and withhold bendamustine and rituximab.</p> <p>Toxic epidermal necrolysis has been reported with L-asparaginase, chlorambucil, cladribine, cytarabine, docetaxel, doxorubicin, gemcitabine, methotrexate, mithramycin, pemetrexed, procarbazine, and 6-mercaptopurine.</p> | <p>Duvelisib, gefitinib</p> <p>Vemurafenib: Toxic epidermal necrolysis has been observed. Discontinue the drug permanently.</p> | Aldesleukin (IL-2), atezolizumab, cetuximab, denileukin, durvalumab, ipilimumab, mogamulizumab |

(Continued on next page)

**TABLE 21-1.** Cutaneous Reactions to Antineoplastic Agents (*Continued*)

| Cutaneous Reaction              | General Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Chemotherapy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Targeted Therapy                                                                                                                                                                                                                                       | Immunotherapy                                                                                                                                                                                                                                                     |
|---------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Transient erythema or urticaria | Urticaria is characterized as multiple swollen, raised areas on the skin that are intensely itchy and appear primarily on the chest, back, extremities, face, and scalp. It usually occurs within hours of chemotherapy and disappears within a few hours. It may be generalized or local at the site of chemotherapy or along the vein.                                                                                                                                                              | <p>Arsenic trioxide, L-asparaginase, carboplatin, cytarabine, daunorubicin, and prednisolone can cause urticaria.</p> <p>L-asparaginase can cause urticaria, fever, chills, and hypotension (skin testing is advised).</p> <p>Bleomycin can cause erythema over pressure points and hyperpigmentation.</p> <p>Chlorambucil, melphalan, methotrexate, and thiopeta can cause urticaria and angioedema.</p> <p>Cytarabine can cause transient erythema.</p> <p>Doxorubicin can cause an erythematous flare with pruritus at the IV site and along the vein.</p> <p>Oxaliplatin can cause delayed urticaria.</p> | <p>The offending agent may need to be discontinued if the reaction is severe or associated with systemic reactions such as a generalized rash.</p> <p>Dasatinib, ivosidenib, pexidartinib, rucaparib, sunitinib, tivozanib, tucatinib, vemurafenib</p> | <p>Aldesleukin can cause erythema and pruritus that may progress into a pruritic papular rash.</p> <p>IFN alfa-2a and IFN alfa-2b can cause dry, scaling, itchy skin or a pruritic maculopapular reaction.</p> <p>Enfortumab vedotin, ofatumumab, panitumumab</p> |
| Trichomegaly                    | <p>Increased hair growth of the eyelashes and eyebrows is rare but can occur.</p> <p>Trichomegaly is associated with patient discomfort and can lead to corneal abrasions and further ocular complications. Ocular changes may occur within 1–2 weeks of treatment.</p> <p>Trichomegaly can be treated with lash clipping every 2–4 weeks. Referral to an ophthalmologist is indicated for patients with irritation or persistent discomfort. Topical eflornithine cream has been well tolerated.</p> | Gemcitabine                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Erlotinib, gefitinib,                                                                                                                                                                                                                                  | Cetuximab, IFN alfa-2b, panitumumab                                                                                                                                                                                                                               |

(Continued on next page)

**TABLE 21-1.** Cutaneous Reactions to Antineoplastic Agents (*Continued*)

| Cutaneous Reaction | General Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Chemotherapy | Targeted Therapy                                                                                                                                                                                                                                                        | Immunotherapy                                                                                             |
|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|
| Xerosis            | <p>Xerosis is abnormal dryness of the skin, mucous membranes, or conjunctiva.</p> <p>Treatment of mild or moderate xerosis consists of thick moisturizing creams without fragrances or potential irritants. Moisturizers should be occlusive, emollient creams that are generally packaged in a jar or tub rather than a lotion that can be pumped or poured. Specific creams can include urea, colloidal oatmeal, and petroleum-based creams.</p> <p>For scaly areas of xerosis, ammonium lactate or lactic acid creams can be used. Greasy creams may be used on the limbs for better control of xerosis but should be used with caution on the face, chest, and extremely hairy sites because of the risk for folliculitis secondary to occlusion.</p> <p>For more severe xerosis causing inflammation with or without eczema, topical steroid creams may be necessary. Topical retinoids and benzoyl peroxide gels are not recommended because of their drying effect.</p> | –            | <p>Afatinib, axitinib, cabozantinib, dacomitinib, dasatinib, erlotinib, everolimus, gefitinib, imatinib, lapatinib, nilotinib, osimertinib, pazopanib, regorafenib, sorafenib, sunitinib, temsirolimus, trametinib, trametinib, vandetanib, vemurafenib, vorinostat</p> | <p>Alemtuzumab, bexarotene, cetuximab, mogamulizumab, necitumumab, panitumumab, pegylated IFN alfa-2b</p> |

EGFRI—epidermal growth factor receptor inhibitor; 5-FU—5-fluorouracil; GVHD—graft-versus-host disease; IFN—interferon; IL—interleukin; IV—intravenous; SPF—sun protection factor; UV—ultraviolet

*Note.* Based on information from Agensys, 2021; Agios Pharmaceuticals, 2021; Amgen, 2021a, 2021b; Anforth et al., 2015; Ariad Pharmaceuticals, 2020; Array BioPharma, 2020, 2021; Astellas Pharma US, 2019; AstraZeneca Pharmaceuticals, 2020, 2021a, 2021b, 2021c, 2021d; AVEO Pharmaceuticals, 2021; Bayer HealthCare Pharmaceuticals, 2020, 2021; BeiGene USA, 2021; Blueprint Medicines, 2021; Bouché et al., 2005; Boucher et al., 2011; Caccavale & Ruocco, 2017; Camp-Sorrell, 2018; Celgene, 2020; Cephalon, 2016; Chon et al., 2012; Clovis Oncology, 2020; Daiichi Sankyo, 2020; Deciphera Pharmaceuticals, 2021; Degen et al., 2010; Eisai, 2021; Eli Lilly and Company, 2020, 2021; Epizyme, 2020; Fabbrocini et al., 2015; Genentech, 2019, 2020a, 2020b, 2021a, 2021b, 2021c; Genentech & Astellas Pharma US, 2016; GlaxoSmithKline, 2021; Hoffmann-La Roche, 2008; Hospira, 2021; Huang & Anadkat, 2011; ImClone, 2021; Immunomedics, 2021; Janssen Pharmaceuticals, 2020, 2021; Kamil et al., 2010; Kaur & Mahajan, 2015; Kheir et al., 2014; Kyowa Kirin, 2018; Lacouture et al., 2011, 2021; Ligand Pharmaceuticals, 2020; Lupu et al., 2016; MacroGenics, 2020; Merck, 2019, 2020; Morse, 2014; National Cancer Institute, 2021; Novartis Pharmaceuticals, 2020a, 2020b, 2021a, 2021b, 2021c, 2021d; Pfizer, 2020a, 2020b, 2020c, 2021a, 2021b; Potthoff et al., 2011; Prometheus Laboratories, 2019; Puma Biotechnology, 2021; Regeneron Pharmaceuticals, 2021; Reyes-Habito & Roh, 2014b; Rosen et al., 2014; Sanofi-Aventis U.S., 2021; Seattle Genetics, 2019, 2020; Segal & Van Cutsem, 2005; Shi et al., 2016; Sibaud, 2018; Stemline Therapeutics, 2018; Taiho Pharmaceutical, 2019; TG Therapeutics, 2021; Thebeau et al., 2017; Tischer et al., 2017; Tummino et al., 2007; Valentine et al., 2015; Verastem, 2019; Villée et al., 2010; White & Cox, 2006; Wu et al., 2011; Wyeth Pharmaceuticals, 2018.

- darker skin on the palms and soles of the feet.
- (c) Lesions related to hand-foot syndrome are painful and will turn into blisters that peel, leading to a decrease in daily activities.
  - (d) Patients also experience decreased quality of life and changes to their treatment schedule (Williams et al., 2020).
  - (e) The Oncology Nursing Society (ONS) Guidelines<sup>™</sup> for Cancer Treatment–Related Skin Toxicity recommend using cooling procedures for patients who received taxane-based therapy to prevent hand-foot syndrome. Cooling procedures include wearing frozen gloves and socks on the hands and feet during treatment (Williams et al., 2020).
- (3) The clinically descriptive term *toxic erythema of chemotherapy* has been introduced as an easily understood clinical name for numerous entities (Shi et al., 2016).
- (a) Clinical findings of toxic erythema of chemotherapy include areas of erythema that may be accompanied by edema, most often involving the hands, feet, and intertriginous zones, such as the axillae and inguinal folds. The elbows, knees, and ears are less frequently involved (Shi et al., 2016).
  - (b) Patches or plaques typically develop within two days to three weeks following drug administration.
    - i. Associated symptoms of pain, burning, paresthesia, and pruritus are frequently present.
    - ii. Areas of intense erythema can be accompanied by the development of a dusky discoloration, petechiae, or sterile bullae, which erosions can follow.
    - iii. Typically, spontaneous resolution and desquamation occur without specific therapy. If the chemotherapy agent is given again at the same or higher dose, recurrences are possible and may be more intense with higher doses.
    - iv. In some instances, delayed onset of 2–10 months can be seen, particularly in patients receiving lower-dose, continuous IV infusions (Shi et al., 2016).
  - (c) Treatment options for toxic erythema of chemotherapy have been of variable success and include bland emollients, analgesics, cool compresses, topical corticosteroids, and topical antibiotics for erosions. Nurses, oncologists, and dermatologists need to recognize the toxic erythema of chemotherapy and understand that the reaction is not allergic or infectious, thus avoiding unnecessary labeling of drug allergies or use of antimicrobials (Shi et al., 2016).
- b) Epidermal growth factor receptor inhibitors (EGFRIs)
- (1) EGFRIs include targeted agents (e.g., gefitinib, erlotinib, lapatinib, afatinib) and monoclonal antibodies (e.g., cetuximab, panitumumab).
  - (2) EGFRIs are associated with many cutaneous reactions due to the prevention of epidermal keratinocytes from controlling the intercellular signal transduction pathways, which regulate cell proliferation, apoptosis, angiogenesis, adhesion, and motility (Wallner et al., 2016). More than 80% of patients will have a cutaneous reaction from treatment with EGFRIs (Ding et al., 2020).
  - (3) Skin toxicities from EGFRIs include acneiform eruption; xerosis; paronychia; abnormal scalp, facial hair, and eyelash growth; maculopapular rash; and postinflammatory hyperpigmentation (see Figure 21-1). EGFR cutaneous reactions are labeled as PRIDE syndrome (papulopustules and/or paronychia, regulatory abnormalities of hair growth, itching, and dryness due to an EGFRi) (Lupu et al., 2016).
  - (4) Acneiform eruption is the most common reaction associated with EGFRIs and can occur in up to 90% of patients.
    - (a) The rash typically occurs in the first two weeks of therapy, peaking around four to six weeks, and resolves by three to four months after therapy (Williams et al., 2020).
    - (b) The presentation can be divided into four stages, beginning with sensory disturbance accompanied by edema and erythema.

**FIGURE 21-1.** Pustular/Papular Rash Presentations**Papular lesions on the chest****V-shaped papulopustular eruption on the back****Follicular pustules****Confluent pustules on the nose**

*Note.* From "Clinical Signs, Pathophysiology and Management of Skin Toxicity During Therapy With Epidermal Growth Factor Receptor Inhibitors," by S. Segaert and E. Van Cutsem, 2005, *Annals of Oncology*, 16(9), p. 1427 (<https://doi.org/10.1093/annonc/mdi279>). Copyright 2005 by European Society for Medical Oncology. Reprinted with permission.

- (c) Subsequently, the characteristic rash of papules and pustules appears and is predominantly but not exclusively folliculocentric in distribution.
- (d) This is followed by a postinflammatory phase of erythema and telangiectasias.
- (e) For patients with darker skin tone, a fourth phase of postinflammatory hyperpigmentation may be present and can be long lasting.
- (5) Refer to Figure 21-2 for treatment options.
- (6) Patients treated with radiation therapy have an increased risk of developing

severe radiation dermatitis. Prophylactic antibiotics have been shown to prevent the rash (Guggina et al., 2017).

c) Multikinase inhibitors

- (1) The multikinase inhibitors sorafenib and sunitinib cause cutaneous reactions in 74% and 81% of patients, respectively. The pathophysiology is unknown but thought to be related to vessel damage or extravasation of the drug (Reyes-Habito & Roh, 2014b).
- (2) Skin toxicities from multikinase inhibitors include hand-foot skin reaction, rash, pruritus, subungual splinter hemorrhage, yellow skin discoloration, hair depigmenta-

tion, pigment dilution, scrotal erythema, and nail splinter hemorrhage (Shi et al., 2016).

- (3) Hand-foot skin reaction, which differs from the classical hand-foot syndrome seen with nontargeted chemotherapy, presents in the first two to four weeks of treatment with the development of localized, painful, and symmetric erythematous plaques on the palms and soles (Ding et al., 2020).

(a) The incidence of hand-foot skin reaction is 9%–62% and dependent on the drug used for therapy (Williams et al., 2020).

(b) Symptoms of hand-foot skin reaction can include paresthesia, tingling, burning, and painful sensation in the palms and soles.

(c) Prior to treatment, prophylactic measures can be taken, including pretreatment pedicure, orthotic evaluation, reduced exposure of hands and

feet to heat, and avoidance of excessive friction.

(d) Celecoxib has been shown to prevent hand-foot skin reactions caused by capecitabine (Lacouture et al., 2021).

(e) ONS Guidelines for Cancer Treatment–Related Skin Toxicity recommend topical urea and topical steroids and usual skin care to prevent hand-foot skin reaction in patients treated with multikinase inhibitors (Williams et al., 2020).

(f) Treatment of hand-foot skin reaction usually requires dose interruption and reduction.

- (4) Symptoms can be reduced by using cooling or topical agents, such as keratolytics, topical corticosteroids, antiseptic solutions, and topical analgesics (Lacouture et al., 2021).

d) BRAF inhibitors (e.g., dabrafenib, vemurafenib) and multikinase inhibitors (e.g., selumetinib, trametinib)

**FIGURE 21-2.** Recommendations for Prevention and Management of Epidermal Growth Factor Receptor Inhibitor–Induced Rash

#### Multinational Association of Supportive Care in Cancer

##### Preventive/Prophylactic

- Systemic: minocycline 100 mg daily<sup>a</sup> or doxycycline 100 mg BID<sup>b</sup>
- Topical: hydrocortisone 1% cream with moisturizer and sunscreen BID

##### Treatment

- Topical
  - Alclometasone 0.05% cream
  - Fluocinonide 0.05% cream BID
  - Clindamycin 1%
- Systemic
  - Doxycycline 100 mg BID
  - Minocycline 100 mg daily
  - Isotretinoin at low doses of 20–30 mg/day

#### Not Recommended

Acitretin, oil-in-water topical trolamine emulsion, pimecrolimus 1% cream, sunscreen as a single agent, tazarotene 0.05% cream, tetracycline 500 mg BID, vitamin K<sub>1</sub> cream

#### National Comprehensive Cancer Network

##### Preventive/Prophylactic

- Systemic
  - Oral semisynthetic tetracycline agents (doxycycline or minocycline)
  - Doxycycline 100 mg BID in combination with the following topical agents
- Topical: hydrocortisone 1%, skin moisturizer, and sunscreen

##### Treatment

- Topical: Topical steroids and antibiotics, such as clindamycin and erythromycin, may be useful.
- Systemic
  - Oral antibiotics include doxycycline, minocycline, and oxytetracycline.
  - Topical low/moderate steroid
  - Isotretinoin at low doses of 20–30 mg/day

#### Oncology Nursing Society Guidelines™ for Cancer Treatment–Related Skin Toxicity

##### Preventive/Prophylactic

- Systemic<sup>c</sup>: doxycycline, tetracycline, or minocycline
- Topical: Topical steroids and antibiotics may be useful.

##### Treatment

- Systemic: Oral antibiotics include tetracycline, minocycline, and doxycycline.

<sup>a</sup>Minocycline is less photosensitizing.

<sup>b</sup>Doxycycline should be used in patients with renal impairment.

<sup>c</sup>The use of prophylactic antibiotics should be weighed against the possible side effects of antibiotic use. Patient clinical status and preference should also be considered.

BID—twice daily

Note. Based on information from Eaby-Sandy et al., 2012; Lacouture et al., 2011, 2020; Williams et al., 2020.



- (1) Dermatologic side effects are the most common adverse events seen with BRAF inhibitors. Pathophysiology is thought to be a hypersensitivity reaction (Shi et al., 2016).
  - (a) The most common dermatologic side effect is rash, which can be maculopapular, papulopustular, or folliculocentric and often appears on the face, upper torso, and arms.
  - (b) Other cutaneous reactions include photosensitivity, which usually occurs within 24 hours of sun exposure and can include painful blistering.
  - (c) It is important to provide patient education about proper sun protection, including broad-spectrum sunscreen and protective clothing (Russo et al., 2018).
  - (d) Squamoproliferative lesions are common and can present as skin papillomas, verrucous keratosis, and seborrheic keratosis.
  - (e) Vemurafenib or dabrafenib have been associated with keratoacanthomas or squamous cell carcinomas and melanocytic changes with all BRAF inhibitors. Regular dermatologic follow-up is recommended for these patients.
  - (f) Other dermatologic effects include hand-foot skin reaction and altered hair growth. MEK (mitogen-activated extracellular signal regulated kinase) inhibitors have similar cutaneous effects with EGFRIs, including xerosis, pruritus, and papulopustular eruption on the scalp, face, chest, and back (Shi et al., 2016).
- (2) Treatment
  - (a) Treatment for rash includes topical antibiotics, oral antibiotics, and topical corticosteroids.
  - (b) Treatments for squamoproliferative lesions include shave excision and cryotherapy (Shi et al., 2016).
- e) Immunotherapies
  - (1) Cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitors, such as ipilimumab, are commonly associated with rash, usually occurring in the first three to four weeks.
    - (a) The rash is typically erythematous macules and papules that coalesce into thick plaques on the extremities and trunk.
    - (b) Vitiligo also can occur (Russo et al., 2018).
  - (2) The cutaneous adverse effects of programmed cell death protein 1 (PD-1) inhibitors, such as nivolumab and pembrolizumab, and programmed cell death-ligand 1 (PD-L1) inhibitors, such as atezolizumab, include vitiligo, rash, and pruritus, with rash and pruritus being the most common. Cutaneous complications from PD-1 inhibitors are less severe and occur later in therapy than those from CTLA-4 inhibitors.
    - (a) Cutaneous side effects are most often mild and easily managed with supportive care (Russo et al., 2018).
    - (b) Lichenoid rash presents with erythematous papules and plaques on the chest, back, abdomen, and extremities.
    - (c) The most common rash occurring from PD-1 inhibitor therapy is a nonspecific maculopapular rash, occurring most often on the trunk and extremities (see Figures 21-3, 21-4, and 21-5).
    - (d) PD-L1 inhibitors may have a slightly lower incidence of rash than CTLA-4 inhibitors (Sibaud, 2018).
  - (3) Cutaneous side effects occurring with anti-CTLA-4 and anti-PD-1 combination therapies are more frequent, severe, and longer lasting than those occur-

**FIGURE 21-3.** Immunotherapy-Mediated Rash: Metastatic Melanoma



Patient is a 67-year-old woman with metastatic melanoma status post 3 doses of pembrolizumab with diffuse rash to bilateral legs.

Note. Image courtesy of Johns Hopkins Hospital. Used with permission.



**FIGURE 21-4.** Immunotherapy-Mediated Rash: Merkel Cell Carcinoma



Patient is a 71-year-old man with Merkel cell carcinoma status post 22 doses of every-3-week pembrolizumab.

Note. Image courtesy of Johns Hopkins Hospital. Used with permission.

ring with single-agent therapy (Sibaud, 2018).

- (4) Treatment includes topical corticosteroids for low-grade eruptions and systemic corticosteroids for high-grade eruptions and antihistamines. Treatment interruption is rare (Russo et al., 2018).
- f) Combination radiation and targeted therapy
  - (1) Significant in-field toxicity can occur when radiation therapy and targeted agents are given concomitantly (Guggina et al., 2017).
  - (2) The best prevention for radiation dermatitis is to wash with soap and water. This can reduce the risk of radiation dermatitis by half (Lacouture, 2015).
  - (3) Topical nonsteroidal agents and moisturizers can significantly reduce discomfort, redness, and itching (Lacouture, 2015).
  - (4) Radiation recall dermatitis is an acute skin inflammatory reaction at the site of a previously treated radiation field that presents similarly to radiation dermatitis with erythema, edema, vesicles, or desquamation.
    - (a) It is most often caused by chemotherapy agents, especially conventional

chemotherapy agents, but can also occur with targeted agents (Laird et al., 2021).

- (b) Chemotherapy agents associated with radiation recall include arsenic trioxide, bleomycin, capecitabine, cyclophosphamide, cytarabine, dactinomycin, daunorubicin, docetaxel, doxorubicin (free and liposomal), etoposide, 5-FU, gemcitabine, hydroxyurea, idarubicin, lomustine, melphalan, methotrexate, paclitaxel, pemetrexed, tamoxifen, and vinblastine (Laird et al., 2021).

- (5) See Figures 21-6 through 21-9 for examples of specific cutaneous manifestations of EGFR- and chemotherapy-induced toxicities.

### 3. Assessment

- a) Accurate grading of dermatologic adverse events is necessary for drug toxicity determination, inte-

**FIGURE 21-5.** Immunotherapy-Mediated Rash: Full-Body Rash



Patient is a 59-year-old man with prostate cancer with biopsy-proven immune-mediated full-body rash after 4 doses of a PD-1 inhibitor, with oral mucositis requiring steroids and discontinuation of immunotherapy.

Note. Image courtesy of Johns Hopkins Hospital. Used with permission.

grant comparisons, and supportive grading scale. The *Common Terminology Criteria for Adverse Events* is widely accepted throughout the oncology community as the standard classification and severity grading scale for adverse events in cancer therapy clinical trials and other oncology settings (National Cancer Institute Cancer Therapy Evaluation Program, 2017; see Table 21-2). However, it was not explicitly designed for the newer agents and may result in underreporting and poor grading of specific adverse events (Wallner et al., 2016).

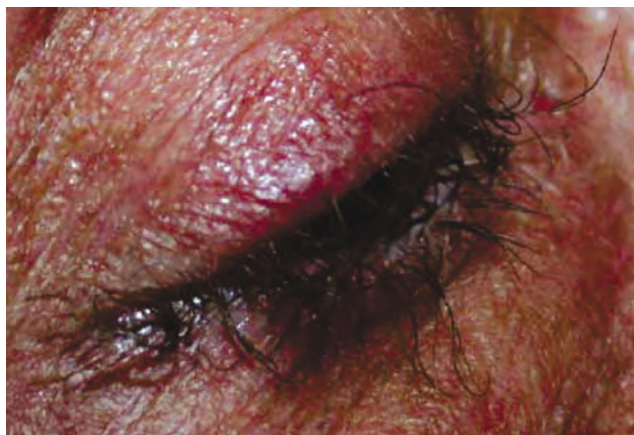
- b) The Multinational Association of Supportive Care in Cancer study group has proposed a new grading scale for EGFR-induced dermatologic adverse events. The organization believes that a class-specific grading scale is needed to help standardize assessment and improve reporting of these dermatologic adverse events (Lacouture, 2015).

#### 4. Collaborative management

##### a) General management

- (1) Prior to initiation of therapy, a full medical history should be taken, including a history of prior or active skin diseases.
  - (a) Partner with an interprofessional team and refer patients to a dermatologist if necessary.
  - (b) Provide patient education regarding reporting any adverse events (Thebeau et al., 2017).
  - (c) Multiple tools are available to assess the impact of cutaneous side effects

**FIGURE 21-6.** Trichomegaly



Note. From "Clinical Signs, Pathophysiology and Management of Skin Toxicity During Therapy With Epidermal Growth Factor Receptor Inhibitors," by S. Segal and E. Van Cutsem, 2005, *Annals of Oncology*, 16(9), p. 1428 (<https://doi.org/10.1093/annonc/mdi279>). Copyright 2005 by European Society for Medical Oncology. Reprinted with permission.

**FIGURE 21-7.** Paronychia of the Nail

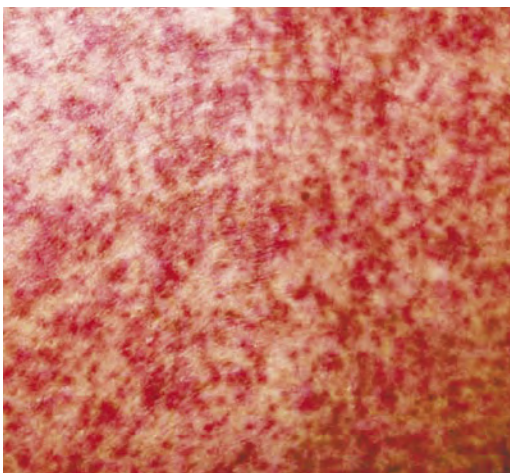


Note. From "Clinical Signs, Pathophysiology and Management of Skin Toxicity During Therapy With Epidermal Growth Factor Receptor Inhibitors," by S. Segal and E. Van Cutsem, 2005, *Annals of Oncology*, 16(9), p. 1428 (<https://doi.org/10.1093/annonc/mdi279>). Copyright 2005 by European Society for Medical Oncology. Reprinted with permission.

on overall quality of life, including the Skindex-16, Skindex-29, and Functional Assessment of Cancer Therapy (FACT)-RGFRI-18 (Tischer et al., 2017).

- (2) Skin reactions are associated with significant morbidity and can lead to dose reductions or premature discontinuation of chemotherapy.
  - (a) The adverse effect of cutaneous reactions on quality of life is only beginning to be understood.
  - (b) Patient-reported outcome questionnaires should be included in routine clinical care to improve the accuracy of reported adverse events (Tischer et al., 2017).
- (3) Treatment of rash is largely dependent on symptoms. Intervention should be recommended based on the severity of the symptoms, with the goal of alleviation or minimization (Thebeau et al., 2017).
- (4) Instruct patients to avoid sun exposure.
  - (a) Patients should apply sunscreen daily to exposed skin areas regardless of the season.
  - (b) Sunscreens with the following characteristics are recommended: hypoallergenic, high SPF (at least 30), para-aminobenzoic acid (PABA) free, ultraviolet A and B protection (broad spectrum), and containing zinc oxide or titanium dioxide.

- (c) Recommend that patients wear a hat and protective clothing for sun protection (Russo et al., 2018).
- b) Secondary infection
  - (1) Secondary bacterial, viral, or fungal infection occurs in 40% of patients taking EGFRIs.
  - (2) Providers should have a low threshold for sending cultures of any lesions with signs of infection, such as discharge.
  - (3) Although secondary infections can occur in any patient with cutaneous toxicity, they are most common with EGFRi rashes (Lacouture et al., 2021).
- c) Rash and response/survival
  - (1) Incidence and severity of papulopustular rashes are associated with a better prognosis, and therefore, are considered to predict tumor response to the EGFRi. Studies addressing EGFRi-induced rash suggest that its severity is a surrogate marker for the efficacy of therapy (Tischer et al., 2017).
  - (2) Data suggest a correlation of rash incidence and severity with clinical response and increased survival time, leading investigators to implement dose-to-rash strategies. An EGFRi dose is progressively escalated until a rash of a specified grade appears. A consistent relationship between rash and response has not been observed

**FIGURE 21-8. Hyperpigmentation**

Note. From "Clinical Signs, Pathophysiology and Management of Skin Toxicity During Therapy With Epidermal Growth Factor Receptor Inhibitors," by S. Segaert and E. Van Cutsem, 2005, *Annals of Oncology*, 16(9), p. 1429 (<https://doi.org/10.1093/annonc/mdi279>). Copyright 2005 by European Society for Medical Oncology. Reprinted with permission.

**FIGURE 21-9. Fissure**

Note. From "Clinical Signs, Pathophysiology and Management of Skin Toxicity During Therapy With Epidermal Growth Factor Receptor Inhibitors," by S. Segaert and E. Van Cutsem, 2005, *Annals of Oncology*, 16(9), p. 1428 (<https://doi.org/10.1093/annonc/mdi279>). Copyright 2005 by European Society for Medical Oncology. Reprinted with permission.

- with all EGFRIs studied in clinical trials (Tischer et al., 2017).
- d) Psychosocial issues
  - (1) Skin toxicities from antineoplastic therapy can significantly impact physical, emotional, and social functions.
    - (a) Patients are at risk for low self-esteem, altered self-image, depression, anxiety, and vulnerability.
    - (b) These side effects may interfere with treatment adherence, but patients may accept them as part of their experience with cancer or as a sign of response to therapy (Williams et al., 2020).
  - (2) Cutaneous toxicity effects on quality of life (Charalambous & Charalambous, 2016)
    - (a) Loss of dignity
    - (b) Hopelessness
    - (c) Living in fear
    - (d) Isolation
    - (e) Feeling insecure
    - (f) Loss of independence
- 5. Patient and family education
  - a) Instruct patients about the potential treatment-related symptoms of dermatologic toxicities as part of supportive measures (Thebeau et al., 2017; Wallner et al., 2016).
  - b) Include information about the potential toxicities associated with the agent.
  - c) Provide information on preventive and management measures, such as avoiding topical products



**TABLE 21-2.** Common Terminology Criteria for Adverse Events Grading Relevant to Targeted Therapy–Associated Dermatologic Toxicity

| Adverse Event  | Grade                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                    |                                                                                                                                                                           |                                                                                                                                                                                                                                      |       |
|----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|
|                | 1                                                                                                                                                                                                                                         | 2                                                                                                                                                                                                                                                                  | 3                                                                                                                                                                         | 4                                                                                                                                                                                                                                    | 5     |
| Alopecia       | Hair loss of < 50% of normal for that individual that is not obvious from a distance but only on close inspection; a different hairstyle may be required to cover the hair loss but it does not require a wig or hair-piece to camouflage | Hair loss of ≥ 50% of normal for that individual that is readily apparent to others; a wig or hair-piece is necessary if the patient desires to completely camouflage the hair loss; associated with psychosocial impact                                           | –                                                                                                                                                                         | –                                                                                                                                                                                                                                    | –     |
| Dry skin       | Covering < 10% BSA and no associated erythema or pruritus                                                                                                                                                                                 | Covering 10%–30% BSA and associated with erythema or pruritus; limiting instrumental ADL                                                                                                                                                                           | Covering > 30% BSA and associated with pruritus; limiting self-care ADL                                                                                                   | –                                                                                                                                                                                                                                    | –     |
| Paronychia     | Nail fold edema or erythema; disruption of the cuticle                                                                                                                                                                                    | Localized intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral); nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL                                      | Operative intervention indicated; IV antibiotics indicated; limiting self-care ADL                                                                                        | –                                                                                                                                                                                                                                    | –     |
| Pruritus       | Mild or localized; topical intervention indicated                                                                                                                                                                                         | Widespread and intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL                                                                          | Widespread and constant; limiting self-care ADL or sleep; systemic corticosteroid or immunosuppressive therapy indicated                                                  | –                                                                                                                                                                                                                                    | –     |
| Rash acneiform | Papules and/or pustules covering < 10% BSA, which may or may not be associated with symptoms of pruritus or tenderness                                                                                                                    | Papules and/or pustules covering 10%–30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL; papules and/or pustules covering > 30% BSA with or without mild symptoms | Papules and/or pustules covering > 30% BSA with moderate or severe symptoms; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated | Life-threatening consequences; papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated | Death |

(Continued on next page)

**TABLE 21-2.** Common Terminology Criteria for Adverse Events Grading Relevant to Targeted Therapy–Associated Dermatologic Toxicity (*Continued*)

| Adverse Event      | Grade                                                                                            |                                                                                                                                                                                      |                                                                                             |   |   |
|--------------------|--------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|---|---|
|                    | 1                                                                                                | 2                                                                                                                                                                                    | 3                                                                                           | 4 | 5 |
| Rash maculopapular | Macules/papules covering < 10% BSA with or without symptoms (e.g., pruritus, burning, tightness) | Macules/papules covering 10%–30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL; rash covering > 30% BSA with or without mild symptoms | Macules/papules covering > 30% BSA with moderate or severe symptoms; limiting self-care ADL | – | – |

ADL—activities of daily living; BSA—body surface area; IV—intravenous

Note. From *Common Terminology Criteria for Adverse Events* [v5.0], by National Cancer Institute Cancer Therapy Evaluation Program, 2017 ([https://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/docs/CTCAE\\_v5\\_Quick\\_Reference\\_5x7.pdf](https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf)). In the public domain.

with fragrance or alcohol and using mild soaps, cream-based moisturizers, and broad-spectrum sunscreen (Williams et al., 2020).

- d) Ensure that family and other support systems (e.g., friends, clergy, visiting nurses, home-care personnel) can encourage patients to help rebuild their self-esteem and self-belief. Discuss the potential for anxiety or depression.
- e) Perform follow-up phone calls to promote communication with patients regarding their treatment experience and provide an opportunity for nurses to educate and give supportive care.

## B. Alopecia

### 1. Overview

- a) Chemotherapy-induced alopecia is one of the most common and distressing side effects of chemotherapy.
- b) Hair loss has been identified as the most troubling aspect of chemotherapy by 58% of patients (Rubio-Gonzalez et al., 2018).
- c) The psychosocial distress associated with chemotherapy-induced alopecia can lead to treatment disruptions.
- d) A portion of these patients may choose not to receive chemotherapy because of an intense fear of this side effect (Ross & Fischer-Carlidge, 2017).
- e) In young adults aged 18–38 years, men and women reported equally negative experiences related to chemotherapy-induced alopecia (Chon et al., 2012).
- f) Chemotherapy-induced alopecia most commonly occurs on the scalp; however, it can occur any-

where on the body, including facial (e.g., beards, eyebrows, eyelashes), axillary, and pubic hair.

- g) Chemotherapy-induced alopecia negatively affects perceptions of body image, sexuality, and self-esteem (Lacouture et al., 2021).

### 2. Pathophysiology

- a) The pathobiology of the response of human hair follicles to chemotherapy remains largely unknown.
- b) Cells responsible for hair growth have high mitotic and metabolic rates, and specific cytotoxic agents disrupt the proliferative phase of hair growth.
- c) Approximately 90% of hair follicles on the scalp are in the anagen (growth) phase of the hair cycle at any given time (Rubio-Gonzalez et al., 2018).
- d) Telogen effluvium and anagen effluvium are the two major types of chemotherapy-induced alopecia.
  - (1) Telogen effluvium involves less than 50% of the scalp and results in hair thinning.
    - (a) Hair enters the telogen (resting) phase and results in shedding three to four months after drug administration.
    - (b) Antineoplastic drugs that can cause this type of alopecia are methotrexate, 5-FU, and retinoids (Paus et al., 2013).
  - (2) Anagen effluvium is the most common form of chemotherapy-induced alopecia.
    - (a) Because most hair follicles are in the anagen (growth) phase, chemother-

apy damages these rapidly growing cells, damaging the inner root sheath cells or the hair shaft integrity.

- (b) The hair shaft is no longer anchored and falls out easily or breaks off at the scalp. Hair falls out spontaneously or during washing or combing.
- (c) Chemotherapy agents such as cyclophosphamide, daunorubicin, doxorubicin, etoposide, ifosfamide, and paclitaxel are associated with this type of damage.
- (d) The hairs remain in the telogen phase after damage occurs until the chemotherapy is completed, at which time they can enter the anagen phase again, and hair regrowth resumes (Paus et al., 2013).

### 3. Incidence

- a) The average incidence of chemotherapy-induced alopecia is approximately 65% of patients and varies depending on the agents used (Williams et al., 2020). The overall risk is lower in patients receiving targeted therapies, with an incidence of 14.7% (Belum et al., 2015).
- b) The extent of alopecia depends on the mechanism of action of the drug, administration route, drug dose, serum half-life, duration (e.g., bolus vs. continuous infusion), the response of the patient, use of combination chemotherapy, and condition of the hair prior to treatment (Rubio-Gonzalez et al., 2018).

### 4. Risk factors

- a) Type of antineoplastic drugs administered
  - (1) The drugs that present the highest risk of alopecia are camptothecins, cyclophosphamide, daunorubicin, docetaxel, doxorubicin, epirubicin, etoposide, ifosfamide, paclitaxel, and vinorelbine (Lacouture et al., 2021; see Table 21-3).
  - (2) Combination chemotherapy is associated with a higher incidence of alopecia than single-agent therapy (Fabbrocini et al., 2015).
  - (3) Molecularly targeted agents, including EGFR antibodies, BRAF inhibitors, cyclin-dependent kinase inhibitors, and Hedgehog pathway inhibitors, have been associated with diffuse alopecia that is generally reversible (Rubio-Gonzalez et al., 2018).
  - (4) Multitargeted tyrosine kinase inhibitors (e.g., sorafenib, sunitinib) have been associated with alopecia, although the inci-

dence is lower than with chemotherapy (Lacouture, 2015).

- b) Certain noncytotoxic medications (e.g., propranolol hydrochloride, heparin sodium, lithium carbonate, prednisone, vitamin A, androgen preparations)
  - c) Certain medical conditions (e.g., hypothyroidism, aging)
  - d) Poor hair condition before cytotoxic treatment
  - e) Concomitant or previous radiation therapy to the head (local effect)
5. Clinical manifestations
- a) Scalp dryness, soreness, pruritus, and rash can occur before, during, or after hair loss.
  - b) Expected time frame and pattern (Lacouture et al., 2021)
    - (1) Chemotherapy-induced alopecia usually begins approximately one to three weeks after administration of the drug. Regrowth usually begins two to three months after completion of therapy.
    - (2) Pattern: Hair loss tends to occur first on the crown and sides of the head above the ears.
    - (3) Chemotherapy-induced alopecia generally is reversible.
    - (4) Regrown hair may demonstrate changes in color, structure, or texture, and in some patients, hair density may continue to be reduced after treatment.
    - (5) Persistent chemotherapy-induced alopecia can occur following chemotherapy and is defined as the absent or suboptimal hair growth continuing six months after the completion of chemotherapy. It can occur with high-dose busulfan and cyclophosphamide following hematopoietic stem cell transplantation, radiation, and taxane treatment (Silva et al., 2020).
6. Assessment (see Table 21-2)
7. Collaborative management: Alopecia is a constant reminder of disease and greatly affects the sense of self. Patients may experience privacy issues because alopecia often is associated with cancer.
- a) Currently, no approved pharmacologic treatment is available to prevent alopecia caused by cytotoxic therapy.
    - (1) Multiple agents have shown to be beneficial as adjunctive therapy, such as topical minoxidil, topical bimatoprost, and calcitriol (Rubio-Gonzalez et al., 2018).
    - (2) The ONS Guidelines for Cancer Treatment-Related Skin Toxicity recommend using topical minoxidil as a potential therapy to reduce or shorten

**TABLE 21-3.** Risk of Chemotherapy-Induced Alopecia for Antineoplastic Agents

| Classification          | High Risk                                                                                                                                                                                | Moderate Risk                                                                                                                                                      | Mild Risk                                                                                                                                                                                           |
|-------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chemotherapy agents     | Cyclophosphamide<br>Daunorubicin<br>Docetaxel<br>Doxorubicin<br>Epirubicin<br>Eribulin<br>Etoposide<br>Ifosfamide<br>Irinotecan<br>Ixabepilone<br>Paclitaxel<br>Topotecan<br>Vinorelbine | Amsacrine<br>Busulfan<br>Carboplatin (area under the<br>plasma concentration<br>versus-time curve 5–6)<br>Cytarabine<br>Gemcitabine<br>Methotrexate<br>Oxaliplatin | Bleomycin<br>Capecitabine<br>Carboplatin (weekly)<br>Cisplatin<br>Cyclophosphamide (oral)<br>5-Fluorouracil<br>Fludarabine<br>Hydroxyurea<br>Mitoxantrone<br>Thiotepa<br>Vinblastine<br>Vincristine |
| Immunotherapy agents    | –                                                                                                                                                                                        | Cetuximab                                                                                                                                                          | Brentuximab                                                                                                                                                                                         |
| Targeted therapy agents | Sorafenib<br>Vismodegib                                                                                                                                                                  | Dabrafenib<br>Regorafenib<br>Vemurafenib                                                                                                                           | Afatinib<br>Axitinib<br>Dasatinib<br>Nilotinib<br>Pazopanib<br>Trametinib                                                                                                                           |

This table may not include all antineoplastics that cause cutaneous toxicities.

Note. Based on information from Mir-Bonafé et al., 2019; Rugo et al., 2017.

chemotherapy-induced alopecia (Williams et al., 2020).

*b) Scalp cooling*

- (1) Scalp cooling is a strategy created to prevent or limit chemotherapy-induced alopecia. It is routinely used in more than 30 countries to prevent chemotherapy-induced alopecia, with reports of response in 50%–80% of patients.
- (2) Scalp cooling is the only intervention that significantly reduces the risk of chemotherapy-induced alopecia. Seven out of eight randomized clinical trials showed a significant advantage for patients who used scalp cooling (Lacouture et al., 2021).
  - (a) The process works by inducing vasoconstriction and decreased follicle metabolism. The decreased blood flow to the hair follicles limits the uptake of the chemotherapy agents. Decreased metabolism makes the follicles less susceptible to damage from the chemotherapy agent.
  - (b) Most patients studied had breast cancer (Ross & Fischer-Carlidge, 2017). A recent prospective cohort study conducted at five U.S. medical centers on women with breast

cancer found that scalp cooling was associated with less hair loss four weeks after the final dose of chemotherapy. The study also found that quality-of-life measures were better in the group that received scalp cooling (Rugo et al., 2017).

- (c) Contraindications exist for scalp cooling and include patients with known hematologic malignancies, lack of safety data, and patients with cold sensitivity, cold agglutinin disease, cryoglobulinemia, and cryofibrinogenemia. Patients may experience headaches, nausea, dizziness, excessive coldness, or feelings of claustrophobia (de Barros Silva et al., 2020).
- (d) Four systematic reviews looking at the percentage of successful hair preservation showed 10%–100% success rates, with the majority around 50% (Ross & Fischer-Carlidge, 2017). Another systematic review found that scalp cooling decreased the relative risk of alopecia by 43% (Rugo & Voigt, 2018).
- (e) The U.S. Food and Drug Administration approved the Digni-



Cap® Paxman® Scalp Cooling Systems in patients with solid tumors (Fischer-Carlidge et al., 2018). Scalp cooling typically begins 30 minutes prior to therapy for the skin temperature to be at its lowest point before the drug enters the hair follicles. Cooling continues throughout therapy and for some time after therapy, depending on the chemotherapy regimen (de Barros Silva et al., 2020).

i. Preparation for scalp cooling includes wetting the hair to improve conduction.

- Healthcare providers need to consider the differences in hair types of ethnicities that may impact proper preparation and efficacy (Araoye et al., 2020).
- The effectiveness of scalp cooling is impacted by cap-scalp contact.
- Areas without proper contact are not protected.
- Curly or kinky hair can become bulkier when wet, making it more challenging to get cap-scalp contact.

ii. Disparities in access to scalp cooling treatments are important to recognize.

- Healthcare providers need to identify potential barriers, such as patient awareness, financial limitations, and geographic access.
- The nearest scalp cooling center is often located more than 50 miles from most chemotherapy infusions, significantly limiting access.
- Financial barriers also restrict use. Medicaid and Medicare do not cover scalp cooling, and private insurance coverage is limited.
- High out-of-pocket costs can restrict use (Singer et al., 2020).

(3) The National Comprehensive Cancer Network (2021) Clinical Practice Guidelines in Oncology recommend scalp cooling treatments for the prevention (category

2A) of chemotherapy-induced alopecia in patients with breast cancer.

(4) The ONS Guidelines for Cancer Treatment-Related Skin Toxicity recommend scalp cooling to prevent chemotherapy-induced alopecia. For patients treated at facilities without access to a cooling system, an ice cap can be used as a prevention method; however, this method is less effective (Williams et al., 2020).

#### 8. Patient and family education

a) Ask patients to verbalize feelings related to hair loss. Increasing their knowledge may give them a sense of control as their appearance changes (Ishida et al., 2015).

b) Advise patients and caregivers about the following (Can et al., 2017):

(1) The cause of alopecia and the time frame of hair loss and regrowth

(2) Strategies to manage hair loss and regrowth

(a) Use baby shampoo with a neutral pH balance.

(b) Avoid using permanent waves, bleach, and coloring agents on hair, vigorous brushing, hot rollers, and excessive heat with hairdryers.

(c) Avoid excessive brushing or combing. Use a soft brush or a wide-tooth comb.

(d) Consider cutting hair in a short style or shaving the head if not participating in scalp cooling (Fabbrocini et al., 2015).

(e) Protect the scalp from the cold and sun with hats, scarves, wigs, and sunscreen. Consider cotton head coverings.

(f) Instruct patients that new hair that grows after completion of therapy may differ from the original hair in color or texture.

(3) Local resources for support (e.g., wig salons, scarf and turban catalogs, scalp cooling locations, support groups)

(a) Look Good Feel Better is a program offered by the Look Good Feel Better Foundation through community organizations, such as the American Cancer Society, that provides guidance and support regarding wigs and other head coverings, makeup, and skin care (Look Good Feel Better Foundation, n.d.).

- (b) Computerized imaging programs to simulate baldness and the look of various types and colors of wigs may be helpful and decrease distress related to hair loss (Chon et al., 2012).
- (c) The Rapunzel Project is a nonprofit organization that aims to increase awareness of scalp cooling therapy. They offer information and resources related to scalp cooling and a list of locations by state (Rapunzel Project, 2021).
- (4) A wig may be covered by insurance, which will help to defray costs. A prescription for a hair prosthesis may be required.
  - (a) Wigs can be synthetic or made of human hair, with the latter being more expensive. Representatives at salons or stores who specialize in wigs can discuss the pros and cons of each type of wig with patients. Synthetic wigs may be damaged by excessive heat during styling. Manufacturer care guidelines should be followed.
  - (b) Wig specialists may have an easier time matching a wig to a patient's usual style if the patient consults the stylist before hair loss begins or provides pictures. It may be helpful to preserve a portion of hair prior to complete hair loss to allow for color and texture matching.
  - (c) If a wig is purchased prior to hair loss, it should be adjustable to decrease the size as the hair loss occurs (Look Good Feel Better Foundation, n.d.).
  - (d) A variety of scarves and turbans are available and assist with protecting the scalp and preventing heat loss.

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## CHAPTER 22

# Endocrine Toxicities

### A. Overview

1. Diverse modalities are currently being used to treat cancer, including cytotoxic chemotherapies, targeted therapies, cellular therapies, and immunotherapies (Rivera et al., 2020).
2. Antineoplastic therapies can cause many adverse events, endocrine toxicities, and endocrinopathies.
3. Endocrinopathies are a dysfunction in the endocrine system that can be transient or permanent (Ravi & Gang, 2019).
4. Aside from steroids administered as part of a chemotherapy regimen, many chemotherapies, targeted therapies, hormones, and immunotherapy agents have been shown to cause hyperglycemia.
5. Targeted therapies cause endocrine disorders and endocrinopathies primarily related to the thyroid.
6. Endocrinopathies are associated with immunotherapy.
  - a) Pancreas, adrenal, thyroid, and pituitary glands are the endocrine organs most commonly affected by immune checkpoint inhibitors (Sznol et al., 2017; Wright et al., 2021).
  - b) Adverse effects include hyperthyroidism, hypothyroidism, hypophysitis, panhypopituitarism, hyperglycemia (diabetes), myxedema, and adrenal insufficiency.
  - c) Most of these are associated with repeated administration of immunotherapy agents.
7. These side effects have a diverse and nonspecific nature.
  - a) They may often go unnoticed and, therefore, underreported, underdiagnosed, and undertreated.
  - b) It is important to remain vigilant and ensure that patients are evaluated for these endocrine disorders prior to, during, and following treatment.
8. Although endocrinopathies may not be considered the most common adverse side effects of antineoplastics, they have been associated with the following:
  - a) Mammalian target of rapamycin inhibitors

- b) Recombinant human interferon alpha
- c) Cytokine interleukin (IL)-2
- d) Tyrosine kinase inhibitors (TKIs)
- e) Glucocorticoids
- f) Checkpoint inhibitors: These therapies upregulate and engage the immune system to destroy tumor cells (González-Rodríguez & Rodríguez-Abreu, 2016; Shariff et al., 2019; see Table 22-1).
  - (1) Cytotoxic T-lymphocyte antigen 4 (CTLA-4)
  - (2) Programmed cell death protein 1 (PD-1)
  - (3) Programmed cell death-ligand 1 (PD-L1)

### B. Drug-specific endocrinopathies

1. Mammalian target of rapamycin inhibitors
  - a) Hyperglycemia is associated with the mammalian target of rapamycin inhibitors (Dy & Adjei, 2013; Hwangbo & Lee, 2017; Kezic et al., 2018; Shariff et al., 2019).
  - b) This category of drugs includes rapamycin, sirolimus, everolimus, and temsirolimus.
  - c) Pathophysiology
    - (1) Decrease in glucose-stimulated insulin secretion from beta cells
    - (2) Increase in apoptosis of beta cells and reduction in mass
    - (3) Increase in peripheral insulin resistance and glucose intolerance
    - (4) Promotion of gluconeogenesis in the liver and hepatic glucose production
  - d) Incidence
    - (1) Hyperglycemia has been found to occur in 12% of patients treated with everolimus and 11% of those treated with temsirolimus.
    - (2) Overall incidence of hyperglycemia is 5.25%–50%.
    - (3) Diabetes due to treatment with everolimus may occur in up to 32% of patients (Kezic et al., 2018).

**TABLE 22-1.** Endocrine Toxicities of Antineoplastics

| Classification                 | Drug                                                 | Side Effects                                                                                                                                                      | Nursing Considerations                                                                                                                                                                                                                                                                                                           |
|--------------------------------|------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Chemotherapy Agents</b>     |                                                      |                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                  |
| Antimetabolites                | Decitabine (Dacogen®)                                | Hyperglycemia observed in clinical trials: 6%–33%                                                                                                                 | Monitor blood glucose, and educate patients and families on the signs and symptoms of hyperglycemia. (MCI Pharma, 2006)                                                                                                                                                                                                          |
| Antitumor antibiotics          | Valrubicin (Valstar®)                                | Hyperglycemia observed in clinical trials: 1%                                                                                                                     | Monitor blood glucose, and educate patients and families on the signs and symptoms of hyperglycemia. (Endo Pharmaceuticals, 2016)                                                                                                                                                                                                |
| Miscellaneous                  | Asparaginase <i>Erwinia chrysanthemi</i> (Erwinaze®) | Glucose intolerance: 5%<br>Hyperglycemia secondary to inhibition of insulin or insulin receptor synthesis: 4%–17%<br>Potentially irreversible glucose intolerance | Monitor blood glucose at baseline and periodically during treatment, and educate patients and families on the signs and symptoms of hyperglycemia. (Porton Biopharma, 2016)                                                                                                                                                      |
|                                | Mitotane (Lysodren®)                                 | Acute adrenal insufficiency                                                                                                                                       | In the presence of acute adrenal injury, hold the drug and administer hydrocortisone; monitor for worsening signs of shock.<br>Inform healthcare providers of planned surgeries.<br>In the presence of adrenal insufficiency, if indicated, initiate steroid replacement therapy with monitoring. (Bristol-Meyers Squibb, 2019b) |
|                                | Omacetaxine (Synribo®)                               | Hyperglycemia (grade 3–4): (11%)<br>Hyperosmolar hyperglycemic                                                                                                    | Avoid use in patients with poorly controlled diabetes mellitus unless good glycemic control is achieved.<br>Monitor blood glucose levels frequently, and educate patients and families on the signs and symptoms of hyperglycemia. (Teva Pharmaceuticals, 2021)                                                                  |
|                                | Pegaspargase (Oncaspar®)                             | Irreversible glucose intolerance<br>Hyperglycemia: 5% (grade 3–4 up to 24%)                                                                                       | Monitor blood glucose levels frequently, and educate patients and families on the signs and symptoms of hyperglycemia. (Sigma-Tau Pharmaceuticals, 2011)                                                                                                                                                                         |
|                                | Vorinostat (Zolinza®)                                | Hyperglycemia: 8.1%                                                                                                                                               | Monitor blood glucose, and educate patients and families on the signs and symptoms of hyperglycemia.<br>Monitor serum glucose every 2 weeks during the first 2 months of treatment and monthly thereafter. (Merck, 2021)                                                                                                         |
| Nitrosoureas                   | Streptozocin (Zanosar®)                              | Hyperglycemia secondary to islet cell inflammation and destruction<br>Impaired glucose tolerance                                                                  | Monitor blood glucose, and educate patients and families on the signs and symptoms of hyperglycemia. (Paladin Labs, 2013)                                                                                                                                                                                                        |
| <b>Targeted Therapy Agents</b> |                                                      |                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                  |
| Small molecule inhibitors      | Axitinib (Inlyta®)                                   | Elevation in thyroid-stimulating hormones in those receiving replacement hormone: 32%<br>Hypothyroidism: 19%<br>Hyperthyroidism: 1%                               | Monitor thyroid-stimulating hormone levels before the initiation of treatment and periodically during treatment. (Pfizer, 2020a)                                                                                                                                                                                                 |

(Continued on next page)



**TABLE 22-1.** Endocrine Toxicities of Antineoplastics (*Continued*)

| Classification                                | Drug                                                                                              | Side Effects                                                                                   | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|-----------------------------------------------|---------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Targeted Therapy Agents (Cont.)</b>        |                                                                                                   |                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Small molecule inhibitors<br>( <i>Cont.</i> ) | Brigatinib<br>(Alunbrig <sup>®</sup> )                                                            | New or worsening hyperglycemia: 43%–56%                                                        | Control blood glucose levels prior to administration. Monitor blood glucose, and educate patients and families on the signs and symptoms of hyperglycemia. In the presence of grade 3 or greater hyperglycemia (> 250 mg/dl or 13.9 mmol/L), hold the drug until adequate hyperglycemic control is achieved. Once hyperglycemic control is achieved, consider reducing to the next lowest dose or permanently discontinuing. (Ariad Pharmaceuticals, 2020)                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                               | Ceritinib<br>(Zykadia <sup>®</sup> )                                                              | Hyperglycemia (grade 3–4): 13%                                                                 | Monitor blood glucose and educate patients and families on the signs and symptoms of hyperglycemia. Withhold drug if patients develop treatment-resistant hyperglycemia > 250 mg/dl. Dose reduction or discontinuation may be required. (Novartis Pharmaceuticals, 2017b)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|                                               | Copanlisib<br>(Aliqopa <sup>®</sup> )                                                             | Hyperglycemia (grade 3–4): 41%<br>Severe hyperglycemia: 2.8%                                   | Optimal blood glucose control is recommended before each infusion. Predose fasting blood glucose 160 mg/dl or higher or random/nonfasting blood glucose of 200 mg/dl or higher: Withhold medication until fasting glucose is 160 mg/dl or lower or random/nonfasting blood glucose is 200 mg/dl or lower. Predose or postdose blood glucose 500 mg/dl or more: On the first occurrence, withhold medication until fasting blood glucose is 160 mg/dl or lower or random/nonfasting blood glucose is 200 mg/dl or lower. Reduce medication from 60 mg to 45 mg and maintain. On subsequent occurrences, withhold medication until fasting blood glucose is 160 mg/dl or lower or a random/nonfasting blood glucose is 200 mg/dl or lower. Reduce medication from 45 mg to 30 mg and maintain. If persistent at 30 mg, discontinue the medication. (Bayer HealthCare, 2017) |
|                                               | Dabrafenib<br>(Tafinlar <sup>®</sup> )                                                            | Hyperglycemia (grade 3–4): 2%–6%                                                               | Monitor blood glucose and educate patients and families on the signs and symptoms of hyperglycemia. (Novartis Pharmaceuticals, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|                                               | Everolimus<br>(Afinitor <sup>®</sup> , Afinitor Dispers <sup>®</sup> tablets for oral suspension) | Hyperglycemia: 75% (grades 3–4: 15%)<br>Diabetes mellitus (new onset and exacerbation): 1%–10% | Monitor blood glucose and educate patients and families on the signs and symptoms of hyperglycemia. The drug may need to be interrupted, dose adjusted, or discontinued based on resolution of hyperglycemia. Monitor fasting serum glucose prior to therapy and periodically during therapy. (Novartis Pharmaceuticals, 2020)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                               | Imatinib mesylate<br>(Gleevec <sup>®</sup> )                                                      | Hypothyroidism reported in post-thyroidectomy patients taking levothyroxine                    | Monitor thyroid-stimulating hormone levels during treatment with these patients. (Novartis Pharmaceuticals, 2016)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                               | Lenvatinib<br>(Lenvima <sup>®</sup> )                                                             | Hypothyroidism: 21%                                                                            | Monitor thyroid function prior to initiating medication and at least monthly during treatment. Treat hypothyroidism according to standard medical practice. (Eisai, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

(Continued on next page)

**TABLE 22-1.** Endocrine Toxicities of Antineoplastics (*Continued*)

| Classification                                | Drug                                 | Side Effects                                                                                                                                                                                               | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-----------------------------------------------|--------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Targeted Therapy Agents (Cont.)</b>        |                                      |                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Small molecule inhibitors<br>( <i>Cont.</i> ) | Lorlatinib (Lorbrena <sup>®</sup> )  | Hyperglycemia: 9%                                                                                                                                                                                          | Assess fasting serum glucose prior to starting medication and regularly during treatment.<br>For grade 3 (greater than 250 mg/dl) glucose despite optimal antihyperglycemic therapy or grade 4: Withhold medication until hyperglycemia is adequately controlled. Resume medication at the next lower dosage.<br>If optimal medical management cannot achieve adequate hyperglycemic control, permanently discontinue the medication.<br>(Pfizer, 2021) |
|                                               | Midostaurin (Rydapt <sup>®</sup> )   | Hyperglycemia: 20%                                                                                                                                                                                         | Monitor blood glucose, and educate patients and families on the signs and symptoms of hyperglycemia.<br>(Novartis Pharmaceuticals, 2017a)                                                                                                                                                                                                                                                                                                               |
|                                               | Pazopanib (Votrient <sup>®</sup> )   | Increased glucose levels: 41%–45%<br>Hypothyroidism: 4%                                                                                                                                                    | Monitor blood glucose, and educate patients and families on the signs and symptoms of hyperglycemia.<br>Monitor thyroid-stimulating hormone levels.<br>(GlaxoSmithKline, 2020)                                                                                                                                                                                                                                                                          |
|                                               | Sorafenib (Nexavar <sup>®</sup> )    | Thyroid-stimulating hormone elevation: 25%–41%                                                                                                                                                             | Monitor thyroid-stimulating hormone levels monthly. Thyroid therapy adjustment may be required.<br>(Bayer HealthCare, 2020)                                                                                                                                                                                                                                                                                                                             |
|                                               | Sunitinib (Sutent <sup>®</sup> )     | Glucose increase: 23%<br>Glucose decrease: 17%<br>Hypothyroidism: 16% with renal cell carcinoma, 7% with primitive neuroectodermal tumors, 4% with gastrointestinal stromal tumor<br>Severe hypothyroidism | Monitor blood glucose, and educate patients and families on the signs and symptoms of hypoglycemia.<br>Monitor thyroid-stimulating hormone levels.<br>Oral levothyroxine and IV methylprednisolone may be initiated to manage severe hypothyroidism.<br>(Pfizer, 2020b)                                                                                                                                                                                 |
|                                               | Temsirolimus (Torisel <sup>®</sup> ) | Hyperglycemia: 89%                                                                                                                                                                                         | Monitor blood glucose, and educate patients and families on the signs and symptoms of hyperglycemia.<br>Test glucose prior to and during treatment.<br>Patients may require insulin or oral hypoglycemic agents for management.<br>(Wyeth Pharmaceuticals, 2015)                                                                                                                                                                                        |
|                                               | Tivozanib (Fotivda <sup>®</sup> )    | Hypothyroidism: 8%<br>Hyperthyroidism: 1%                                                                                                                                                                  | Treat hypothyroidism and hyperthyroidism to maintain an euthyroid state before and during treatment.<br>Monitor thyroid function before initiation and throughout treatment.<br>(AVEO Pharmaceuticals, 2021)                                                                                                                                                                                                                                            |
|                                               | Trametinib (Mekinist <sup>®</sup> )  | Hyperglycemia in combination with dabrafenib (grade 3): 5%                                                                                                                                                 | Monitor blood glucose, and educate patients and families on the signs and symptoms of hyperglycemia.<br>(GlaxoSmithKline, 2014)                                                                                                                                                                                                                                                                                                                         |
|                                               | Vandetanib (Caprelsa <sup>®</sup> )  | Decreased glucose levels: 24%<br>Hypothyroidism: 6%                                                                                                                                                        | Monitor blood glucose, and educate patients and families on the signs and symptoms of hyperglycemia.<br>Consider monitoring thyroid-stimulating hormone levels.<br>(Genzyme, 2018)                                                                                                                                                                                                                                                                      |
|                                               | Vorinostat (Zolinza <sup>®</sup> )   | Hyperglycemia: 8.1%                                                                                                                                                                                        | Monitor serum glucose every 2 weeks during the first 2 months of treatment and monthly thereafter.<br>Educate patients and families on the signs and symptoms of hyperglycemia.<br>(Merck, 2021)                                                                                                                                                                                                                                                        |

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**TABLE 22-1.** Endocrine Toxicities of Antineoplastics (*Continued*)

| Classification                                          | Drug                       | Side Effects                                                                                                                                                                        | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|---------------------------------------------------------|----------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Immunotherapy Agents</b>                             |                            |                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Checkpoint inhibitors: cytotoxic T-lymphocyte antigen 4 | Ipilimumab (Yervoy®)       | Hypothyroidism: 18%–20%<br>Hyperthyroidism: 9%–12%<br>Adrenal insufficiency: 7%–8%<br>Hypophysitis: 4%–9%<br>Diabetes: 2.7%<br>Thyroiditis: 2.7%                                    | Monitor adrenocorticotropic hormone level and thyroid function at baseline and before each dose.<br>Advise patients to contact their healthcare provider immediately for signs or symptoms of hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism, and diabetes mellitus.<br>For grade 3–4 endocrinopathies, withhold until clinically stable or permanently discontinue drug depending on severity. (Bristol-Myers Squibb, 2021b)                                                                                                                                                                                                                    |
| Checkpoint inhibitors: programmed cell death protein 1  | Atezolizumab (Tenzentriq®) | Hypothyroidism: 4.9%–26%<br>Hyperthyroidism: 0.8%–19%<br>Adrenal insufficiency: 0.4%<br>Type 1 diabetes mellitus: 0.3%<br>Thyroiditis: 0.2%<br>Hypophysitis: < 0.1%                 | Monitor thyroid function at baseline and periodically during treatment.<br>For grade 3–4 endocrinopathies, withhold until clinically stable or permanently discontinue drug depending on severity. (Genentech, 2021b)                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|                                                         | Cemiplimab-rwlc (Libtayo®) | Hypothyroidism: 7%<br>Hyperthyroidism: 3.2%<br>Thyroiditis: 0.6%<br>Adrenal insufficiency: 0.4%<br>Hypophysitis: 0.4%<br>Type 1 diabetes mellitus: 0.1%                             | Monitor thyroid function at baseline and periodically during treatment.<br>Type 1 diabetes mellitus can present with diabetic ketoacidosis. Monitor for signs and symptoms of diabetes.<br>For grade 3–4 endocrinopathies: Withhold until clinically stable or permanently discontinue drug depending on severity. (Regeneron Pharmaceuticals, 2021)                                                                                                                                                                                                                                                                                                                   |
|                                                         | Durvalumab (Imfinzi®)      | Hypothyroidism: 8.3%<br>Hyperthyroidism: 2.1%<br>Adrenal insufficiency: 0.5%<br>Thyroiditis: 0.5%<br>Hypophysitis: < 0.1%<br>Type 1 diabetes mellitus: < 0.1%                       | Monitor thyroid function at baseline and periodically during treatment.<br>Type 1 diabetes mellitus can present with diabetic ketoacidosis. Monitor for signs and symptoms of diabetes.<br>For grade 3–4 endocrinopathies: Withhold until clinically stable or permanently discontinue drug depending on severity. (AstraZeneca Pharmaceuticals, 2021)                                                                                                                                                                                                                                                                                                                 |
|                                                         | Nivolumab (Opdivo®)        | Hypothyroidism: 8%–20%<br>Hyperthyroidism: 2.7%–12%<br>Diabetes: 0.9%<br>Hypophysitis: 0.6%–9%<br>Thyroiditis: 0.6%<br>Adrenal insufficiency: 0.4%–8%                               | Monitor thyroid function at baseline and periodically during treatment.<br>Monitor for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated.<br>For grade 3–4 endocrinopathies: Withhold until clinically stable or permanently discontinue drug depending on severity. (Bristol-Myers Squibb, 2021a)                                                                                                                                                                                                                                                                                                        |
|                                                         | Pembrolizumab (Keytruda®)  | Hyperglycemia: 45%<br>Hypothyroidism: 8%–16%<br>Hyperthyroidism: 3%–10%<br>Adrenal insufficiency: 0.8%<br>Hypophysitis: 0.6%<br>Thyroiditis: 0.6%<br>Type 1 diabetes mellitus: 0.2% | For type 1 diabetes mellitus, administer insulin. For severe hyperglycemia, withhold drug and administer antihyperglycemics. Resume once toxicity recovers to grade 0–1.<br>Administer thioamides and beta-blockers as appropriate. Withhold or discontinue drug for severe (grade 3) or life-threatening (grade 4) hyperthyroidism. Resume once toxicity recovers to grade 0–1.<br>Administer corticosteroids and hormone replacement as clinically indicated. For moderate (grade 2) hypophysitis, withhold drug. Withhold or discontinue for severe (grade 3) or life-threatening (grade 4) hypophysitis. Resume once toxicity recovers to grade 0–1. (Merck, 2020) |

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**TABLE 22-1.** Endocrine Toxicities of Antineoplastics (*Continued*)

| Classification                                                             | Drug                                                                     | Side Effects                                                                                                                                                                                                                | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|----------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Immunotherapy Agents (Cont.)</b>                                        |                                                                          |                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Checkpoint inhibitors: programmed cell death-ligand 1                      | Avelumab (Bavencio®)                                                     | Thyroid gland disorder: 6%<br>Hypoparathyroidism/hypothyroidism: 5%–25%<br>Adrenal insufficiency: 0.5%<br>Hyperthyroidism: 0.4%<br>Thyroiditis: 0.2%<br>Disorder of pituitary gland: 0.1%<br>Type 1 diabetes mellitus: 0.1% | For grade 3–4 endocrinopathies: Withhold drug and initiate appropriate medical management of toxicity. Resume once toxicity recovers to grade 0–1 and corticosteroid taper.<br>For persistent grade 2–3 immune-mediated toxicity (lasting 12 weeks or longer): Permanently discontinue drug.<br>For patients who require 10 mg/day or greater prednisone or equivalent for > 12 weeks, permanently discontinue drug. (EMD Serono, 2020)                                                                                                            |
| Cytokines                                                                  | Interferon alfa-2b (Intron-A®)                                           | Diabetes mellitus<br>Thyroid abnormalities (hypo/hyperthyroidism)                                                                                                                                                           | Patients whose glucose levels cannot be maintained with medication should not begin interferon alfa-2b therapy. In patients who develop this condition during therapy, which cannot be controlled with medication, discontinue drug treatment.<br>Discontinuation of interferon therapy has not always reversed dysfunction occurring during treatment. Thyroid-stimulating hormone levels should be evaluated prior to starting interferon alfa-2b, and treatment should be discontinued if patients develop thyroid abnormalities. (Merck, 2017) |
| Immunomodulators                                                           | Lenalidomide (Revlimid®)                                                 | Acquired hypothyroidism: 6.8%                                                                                                                                                                                               | Clinical monitoring of thyroid function is recommended. (Celgene, 2019)                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Monoclonal antibodies: human                                               | Bevacizumab (anti-vascular endothelial growth factor antibody; Avastin®) | Hyperglycemia: 26%                                                                                                                                                                                                          | Monitor blood glucose and educate patients and families on the signs and symptoms of hyperglycemia. (Genentech, 2021a)                                                                                                                                                                                                                                                                                                                                                                                                                             |
|                                                                            | Elotuzumab (Empliciti™)                                                  | Hyperglycemia: 20%–89%                                                                                                                                                                                                      | Monitor blood glucose, and educate patients and families on the signs and symptoms of hyperglycemia. (Bristol-Myers Squibb, 2019a)                                                                                                                                                                                                                                                                                                                                                                                                                 |
|                                                                            | Ramucirumab (Cyramza®)                                                   | Hypothyroidism: < 1%–3%                                                                                                                                                                                                     | Monitor thyroid function during treatment. (Eli Lilly and Company, 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Monoclonal antibody–drug conjugate: cluster of differentiation 30 directed | Brentuximab vedotin (Adcetris®)                                          | Hyperglycemia: 8%                                                                                                                                                                                                           | Hyperglycemia occurred more frequently in patients with high body mass index or diabetes. Monitor serum glucose. If hyperglycemia develops, administer antihyperglycemic medications as clinically indicated. (Seagen, 2020)                                                                                                                                                                                                                                                                                                                       |
| Monoclonal antibody–drug conjugate: nectin-4 directed                      | Enfortumab vedotin-ejfv (Padcev®)                                        | Hyperglycemia: 14%                                                                                                                                                                                                          | Hyperglycemia and diabetic ketoacidosis, including fatal events, occurred in patients with and without preexisting diabetes mellitus. Withhold drug until blood glucose has improved to $\leq 250$ mg/dl. Resume treatment at the same dose level. (Astellas Pharma US, 2021a)                                                                                                                                                                                                                                                                     |
| <b>Miscellaneous Therapies</b>                                             |                                                                          |                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Calcineurin inhibitors                                                     | Tacrolimus (Prograf®)                                                    | Hyperglycemia: 22%–47%<br>New-onset diabetes mellitus: 13%–75% (increased risk in African American and Hispanic transplant recipients)                                                                                      | Monitor blood glucose, and educate patients and families on the signs and symptoms of hyperglycemia. (Astellas Pharma US, 2021b)                                                                                                                                                                                                                                                                                                                                                                                                                   |

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**TABLE 22-1.** Endocrine Toxicities of Antineoplastics (*Continued*)

| Classification                         | Drug                           | Side Effects                                                                                                           | Nursing Considerations                                                                                                                                                                                                                                                                                                                   |
|----------------------------------------|--------------------------------|------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Miscellaneous Therapies (Cont.)</b> |                                |                                                                                                                        |                                                                                                                                                                                                                                                                                                                                          |
| Hormones                               | Lanreotide (Somatuline® depot) | Dysglycemia (hypoglycemia, hyperglycemia, diabetes): 14%<br>Hypothyroidism: < 1%                                       | Blood glucose levels should be monitored when treatment is initiated or when the dose is altered. Antidiabetic treatment should be adjusted accordingly.<br>Thyroid function tests are recommended where clinically indicated.<br>(Ipsen Pharma Biotech, 2019)                                                                           |
|                                        | Leuprolide (Lupron®)           | Diabetes mellitus                                                                                                      | Monitor blood glucose and educate patients and families on the signs and symptoms of diabetes mellitus.<br>(Abbott Laboratories, 2014)                                                                                                                                                                                                   |
|                                        | Octreotide (Sandostatin®)      | Hyperglycemia secondary to inhibition of insulin secretion: 16%<br>Hypothyroidism: 12%<br>Hypoglycemia: 3%             | Monitor blood glucose and educate patients and families on the signs and symptoms of hyper- and hypoglycemia.<br>Baseline and periodic assessments of thyroid function tests are recommended during chronic therapy.<br>Thyroid replacement therapy may be needed in the presence of hypothyroidism.<br>(Novartis Pharmaceuticals, 2008) |
| Steroids                               | Glucocorticoids                | Hyperglycemia secondary to increased hepatic glucose<br>Decreased insulin effectiveness<br>Decreased insulin secretion | Monitor blood glucose, and educate patients and families on the signs and symptoms of hyperglycemia.<br>(Shariff et al., 2019)                                                                                                                                                                                                           |

*Note.* The table is not all inclusive of every agent that causes endocrine toxicities. Review package inserts for dosing and prescribing information.

- e) Risk factors may be similar to those for cancer and include obesity, decreased physical activity, and older age.
  - f) Manifestations: Hyperglycemia usually occurs within the first six weeks of treatment and resolves between doses.
  - g) Assessment: Patients should have fasting blood glucose and hemoglobin A1c levels checked prior to initiating treatment, every two weeks for one month, and then monthly during treatment.
  - h) Prevention and treatment
    - (1) Lifestyle modifications should be made (e.g., caloric restriction, exercise), and antidiabetic medication should be initiated if indicated (American Diabetes Association, 2021).
    - (2) Concurrent use of metformin (biguanides) with rapalogs may help prevent the development of diabetes (Kezic et al., 2018).
    - (3) For patients with a history of hyperglycemia or diabetes, optimize blood glucose control prior to treatment.
    - (4) For blood glucose levels of 250–500 mg/dl, hold the drug temporarily and restart at a decreased dose.
    - (5) For blood glucose greater than 500 mg/dl, discontinue the drug.
  - i) Patient and family education: Educate patients and families to report the signs and symptoms of hyperglycemia (e.g., increased thirst, increased urination, blurred vision).
2. Human interferon alpha
    - a) Hyperthyroidism or hypothyroidism and biphasic thyroiditis are associated with recombinant human interferon alpha used in the treatment of hairy cell leukemia, resected high-risk melanoma, renal cell carcinoma, Kaposi sarcoma, and lymphoma (Bhattacharya et al., 2020; Hauschild et al., 2008; Weber et al., 2015).
    - b) Pathophysiology: The mechanism by which thyroid dysfunction occurs is not fully understood. It is believed to occur due to the expression of the MHC-1 antigen, which causes activation of cytotoxic T cells and results in cellular destruction (Bhattacharya et al., 2020).
    - c) Incidence: Thyroid disorders occur in 2.4%–31% of patients receiving treatment for solid tumors (Bhattacharya et al., 2020).
    - d) Risk factors
      - (1) Presence of thyroid antibodies
      - (2) Preexisting thyroid disease, leading to increased severity of hypothyroidism
    - e) Manifestations
      - (1) Symptoms of hyperthyroidism

- (a) Palpitations
    - (b) Weight loss
    - (c) Diarrhea
    - (d) Cold intolerance
  - (2) Symptoms of hypothyroidism
    - (a) Constipation
    - (b) Heat intolerance
    - (c) Weight gain, which usually occurs 3–12 weeks after initiation of therapy
  - f) Assessment
    - (1) Assess thyroid function (i.e., thyroid-stimulating hormone [TSH] and free thyroxine [ $T_4$ ] and antibodies (i.e., thyroid peroxidase antibodies and thyroglobulin) at induction and maintenance.
    - (2) If thyroid antibodies are present, recheck thyroid function every two months.
    - (3) If not antibody positive, check every six months.
  - g) Prevention and treatment
    - (1) Levothyroxine (1.6 mcg/kg) is used to treat hypothyroidism.
    - (2) Beta-blockers or corticosteroids may also be used.
    - (3) Symptoms may resolve when therapy is discontinued.
    - (4) If thyroid functions do not normalize, therapy should be discontinued.
  - h) Patient and family education
    - (1) Instruct patients and families to report symptoms of hypo- or hyperthyroidism.
    - (2) If thyroid hormone replacement has been initiated, instruct patients to take medication on an empty stomach in the morning.
3. Cytokine IL-2
- a) Thyroiditis is associated with cytokine IL-2 used to treat advanced renal cell carcinoma and melanoma (Bhattacharya et al., 2020; Weber et al., 2015).
  - b) This category of drugs includes aldesleukin.
  - c) Pathophysiology
    - (1) IL-2 increases IL-1, interferon gamma, tumor necrosis factor-alpha, and infiltration of lymphocytes into the thyroid gland.
    - (2) This induces the presence of autoantigens and human leukocyte antigen class II on thyrocytes, resulting in autoimmune destruction.
  - d) Incidence: Approximately 35% of patients may experience hypothyroidism, and 7% may experience hyperthyroidism (Bhattacharya et al., 2020).
  - e) Risk factors: Hypothyroidism is related to the duration of therapy and the presence of thyroid antibodies prior to treatment.
  - f) Manifestations
    - (1) Hyperthyroidism
      - (a) Palpitations
      - (b) Weight loss
      - (c) Diarrhea
      - (d) Cold intolerance
    - (2) Hypothyroidism
      - (a) Weight gain
      - (b) Constipation
      - (c) Heat intolerance
      - (d) Constipation
  - g) Assessment: Routine testing of thyroid hormones (TSH and free  $T_4$ ) should be performed prior to and every two to three months during treatment.
  - h) Prevention and treatment
    - (1) If hypothyroidism is detected before initiation of treatment, hormone replacement therapy should be initiated and treatment delayed for at least two weeks.
    - (2) Hormone replacement therapy should be continued for one year or until levels return to normal. Symptoms resolve upon withholding the drug, usually in 6–10 months.
  - i) Patient and family education
    - (1) Instruct patients and families to report symptoms of hypo- or hyperthyroidism.
    - (2) If thyroid hormone replacement has been initiated, instruct patients to take medication on an empty stomach in the morning.
4. TKIs
- a) This category of drugs includes axitinib, erlotinib, dasatinib, nilotinib, lenvatinib, pazopanib, vandetanib, sorafenib, sunitinib, motesanib, gefitinib, and regorafenib.
  - b) Hyperglycemia and improved blood glucose levels have been associated with TKIs used in treating renal cell carcinoma, hepatocellular carcinoma, pancreatic neuroendocrine tumors, gastrointestinal stromal tumor, medullary thyroid cancer, adenosquamous cell carcinoma of the lung, and small cell cancer (Shariff et al., 2019).
    - (1) Pathophysiology
      - (a) Improved blood glucose is associated with protection from beta cell apoptosis.
      - (b) Hyperglycemia is attributed to the blocking of TKI activity, resulting in insulin resistance.
    - (2) Incidence: Hyperglycemia occurs in 5%–45% of patients treated with TKIs.
    - (3) Assessment: Patients should have fasting blood glucose and hemoglobin A1c levels checked prior to initiating treatment, every two weeks for one month, and then monthly during treatment.

- (4) Lifestyle modifications should be made (e.g., caloric restriction, exercise), and antidiabetic medication should be initiated if indicated (American Diabetes Association, 2021).
  - (5) Patient and family education: Educate patients and families to report signs and symptoms of hyperglycemia (e.g., increased thirst, increased urination, blurred vision) and hypoglycemia (e.g., lightheadedness, dizziness, weakness, palpitations).
- c) Hypothyroidism has been shown to occur with TKIs and increases with time and the number of treatments (Bhattacharya et al., 2020).
- (1) Pathophysiology: TKIs impair the vascularization of the thyroid, induce ischemia, and block vascular growth factor signaling pathways.
  - (2) Incidence: Approximately 14%–70% of patients receiving sunitinib may experience hypothyroidism. Incidence with sorafenib is less frequent (6.3%–27%). Hypothyroidism may occur at 4–92 weeks.
  - (3) Manifestations: Weight gain, constipation, heat intolerance, dry skin, and fatigue can occur.
  - (4) Assessment
    - (a) Routine testing of thyroid hormones (TSH and free  $T_4$ ) should be performed prior to treatment and monthly for the first six months (every two to three months or at the time of clinical symptoms).
    - (b) For patients with preexisting thyroid disease, TSH testing should be performed monthly for the first three months and then every three months for the duration of therapy.
  - (5) Prevention and treatment
    - (a) If hypothyroidism is detected prior to treatment, hormone replacement therapy should be initiated.
    - (b) Hormone replacement therapy should be continued until treatment is completed. At that time, a trial withdrawal can be considered. If symptoms resolve upon withholding of the drug, the medication can be discontinued.
  - (6) Patient and family education
    - (a) Instruct patients and families to report symptoms of hypo- or hyperthyroidism.
    - (b) If thyroid hormone replacement has been initiated, instruct patients to take medication on an empty stomach in the morning.
5. Glucocorticoids
- a) Glucocorticoids are used in cancer treatment as curative agents (in combination with other chemotherapy agents) for chronic lymphocytic leukemia, Hodgkin lymphoma, multiple myeloma, and acute lymphoblastic leukemia. They are also used as antiemetics and anti-inflammatories (Pufall, 2015).
  - b) Glucocorticoids are known to cause the following (Hwangbo & Lee, 2017; Oyer et al., 2006; Shariff et al., 2019; Simmons et al., 2012; Trencce, 2003; van Raalte et al., 2009; Vigneri et al., 2009):
    - (1) Decreased beta cell mass
    - (2) Increased glucose intolerance
    - (3) Decreased insulin effectiveness
    - (4) Increased hepatic glucose output
    - (5) Hyperinsulinemia
    - (6) Decreased beta cell effectiveness and beta cell failure
  - c) This category of drugs includes hydrocortisone, methylprednisolone, prednisone, prednisolone, and dexamethasone.
  - d) Pathophysiology
    - (1) Glucocorticoids inhibit glucose transport and phosphorylation, decreasing available intracellular energy.
    - (2) They impede mitotic cell division.
    - (3) Glucocorticoids inhibit protein synthesis, resulting in apoptotic cell death (Coleman, 1992; Laane et al., 2009; Shariff et al., 2019).
    - (4) Glucocorticoids enhance the effect of glucagon and epinephrine and increase gluconeogenesis.
  - e) Incidence: Approximately 60%–80% of patients treated with corticosteroids will experience hyperglycemia (Shariff et al., 2019).
  - f) Risk factors (Handy et al., 2013; Hwangbo & Lee, 2017)
    - (1) Preexisting diabetes mellitus (prolonged or undiagnosed)
    - (2) Family history of diabetes mellitus
    - (3) Down syndrome
    - (4) Increased age
    - (5) Increased body mass index
    - (6) Central nervous system disease
    - (7) Concurrent administration of tacrolimus, cyclosporine, or L-asparaginase
    - (8) Female sex
    - (9) Ethnicity



g) Manifestations (Cleveland Clinic, 2020; Handy et al., 2013)

(1) Early

- (a) Hyperglycemia (blood glucose greater than 180 mg/dl)
- (b) Dry mouth
- (c) Irritability
- (d) Drowsiness
- (e) Blurred vision
- (f) Polyphagia (increased hunger)
- (g) Dry and itchy skin
- (h) Polydipsia (increased thirst)
- (i) Polyuria (increased urination)
- (j) Fatigue
- (k) Weight loss

(2) Late

- (a) Confusion and disorientation
- (b) Dehydration
- (c) Nausea and vomiting
- (d) Shortness of breath
- (e) Tremor
- (f) Tachycardia
- (g) Elevated systolic blood pressure
- (h) Anxiety
- (i) Seizures
- (j) Coma

h) Assessment

- (1) Monitor blood glucose, both fasting and two hours postprandial (after lunch) (Hwangbo & Lee, 2017).
- (2) Assess for diabetic ketoacidosis. Check electrolytes and urine ketones, calculate the anion gap, and check arterial venous blood gas (Mouri & Badireddy, 2021).
- (3) Check hemoglobin A1c every three to six months (American Diabetes Association, 2021; Mouri & Badireddy, 2021).
- (4) Monitor for glucocorticoid-induced osteoporosis and osteonecrosis (Oray et al., 2016).

i) Prevention and treatment (see Figure 22-1)

j) Patient and family education: The degree of hyperglycemia often is related to the potency and duration of action of the steroid administered.

- (1) For example, hydrocortisone has a short duration of action (2–10 hours) compared to dexamethasone (72 hours).
- (2) Repeated exposure to steroids can result in sustained hyperglycemia, requiring long-term use of antidiabetic medications.

C. Immune checkpoint inhibitor–related endocrinopathies (Bhattacharya et al., 2020; Spain et al., 2016; Vaddepalay et al., 2020; Villadolid & Amin, 2015; Wright et al., 2021)

1. CTLA-4 is a checkpoint protein expressed on the surface of activated T cells that bind to B7 molecules and inhibit T-cell–mediated immune responses.

- a) Ipilimumab is an example of a CTLA-4 inhibitor.
- b) CTLA-4 inhibitors are used to treat renal cell carcinoma, melanoma, hepatocellular cancer, colorectal cancer, metastatic non-small cell lung cancer, and pleural mesothelioma.

2. PD-1 is an immune checkpoint expressed on the surface of activated T cells. Blockade of the PD-1 pathway results in T-cell antitumor activity, leading to the killing of cancer cells.

- a) PD-1 inhibitors include pembrolizumab, nivolumab, cemiplimab, and dostarlimab.
- b) PD-1 inhibitors are used in the treatment of renal cell carcinoma, melanoma, Hodgkin lymphoma, non-small cell lung cancer, small cell lung cancer, B-cell lymphoma, hepatocellular carcinoma, squamous cell carcinoma of the head and neck, urothelial carcinoma, colorectal cancer, Merkel cell carcinoma, cervical cancer, gastric/esophagogastric junction/esophageal cancer, cutaneous squamous cell cancer, endometrial cancer, and triple-negative breast cancer.

3. PD-L1 is expressed on T cells and interacts with B7 molecules, resulting in T-cell inactivation.

- a) PD-L1 inhibitors include atezolizumab, avelumab, and durvalumab.
- b) PD-L1 inhibitors are used to treat urothelial carcinoma, melanoma, hepatocellular carcinoma, non-small cell lung cancer, small cell lung cancer, metastatic Merkel cell carcinoma, and metastatic triple-negative breast cancer.

4. The adverse side effects of CTLA-4, PD-1, and PD-L1 inhibitors are similar. Side effects from CTLA-4 inhibitors are usually dose related; however, there does not appear to be a dose–toxicity relationship between PD-1 and PD-L1 inhibitors.

- a) Hypothyroidism (Dy & Adjei, 2013; González-Rodríguez & Rodríguez-Abreu, 2016; Hattersley et al., 2021; Khan et al., 2017; Spain et al., 2016; Villadolid & Amin, 2015; Wright et al., 2021)

(1) Pathophysiology: The pathophysiology has not been fully elucidated.

- (2) Incidence: Hypothyroidism occurs in 7%–8% of patients treated with PD-1 inhibitors and 3.9% treated with CTLA-4 inhibitors. Incidence is 13.2% with combination PD-1 and CTLA-4 (Barroso-Sousa et al., 2018; Hattersley et al., 2021).

- (3) Risk factors: Adverse events are more common in women and patients with pre-existing antithyroid antibodies.

**FIGURE 22-1.** Glucocorticoid-Induced Hyperglycemia

| Glucocorticoids                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Mechanism                                                                                                                                                                                                                  | Risk Factors                                                                                                                                                                                                                                                                                                             | Characteristics                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Treatments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Hydrocortisone</b> <ul style="list-style-type: none"> <li>• Peak effect: 1 hour</li> <li>• Duration: 2–10 hours</li> </ul> <b>Methylprednisolone</b> <ul style="list-style-type: none"> <li>• Peak effect: 2 hours</li> <li>• Duration: 12–36 hours</li> </ul> <b>Prednisone</b> <ul style="list-style-type: none"> <li>• Peak effect: 4–8 hours</li> <li>• Duration: 12–36 hours</li> </ul> <b>Dexamethasone</b> <ul style="list-style-type: none"> <li>• Peak effect: 20 hours</li> <li>• Duration: 36–72 hours</li> </ul> | Impairs glucose uptake in peripheral tissues<br>Increases hepatic glucose production<br>Stimulates protein catabolism, which increases concentrations of circulating amino acids, providing precursors for gluconeogenesis | Total steroid dose and duration of therapy<br>Preexisting diabetes mellitus (prolonged or undiagnosed)<br>Family history of diabetes mellitus<br>Down syndrome<br>Increased age<br>Increased body mass index<br>Central nervous system disease<br>Concurrent administration of tacrolimus, cyclosporine, or asparaginase | Hyperglycemia due to glucocorticoids usually occurs postprandially. Fasting blood glucose levels are often normal, particularly with once-daily steroid dosing, which may lead to underdiagnosis if labs are only checked in the morning.<br>Blood glucose rises after lunch and throughout the evening.<br>Monitor blood glucose for patients on glucocorticoids 2 hours postprandial.<br>Postprandial hyperglycemia is often the first indication. Hyperglycemia is most common during acute lymphoblastic leukemia induction therapy.<br>It usually spontaneously resolves in most patients who did not previously have diabetes.<br>Hyperglycemia can be associated with diabetic ketoacidosis. | <b>Insulin</b><br><i>Benefits:</i> <ul style="list-style-type: none"> <li>• Few contraindications exist.</li> <li>• Few drug interactions exist.</li> <li>• Frequent adjustments are possible as steroids are tapered.</li> <li>• Type and peak duration can be matched to steroid duration and dosage.</li> <li>• The drug may be administered subcutaneously or intravenously as a continuous infusion.</li> <li>• Long-acting and quick-acting formulations can be combined to provide basal, correctional, and nutritional coverage.</li> <li>• Nutritional insulin will comprise 60%–75% of total daily insulin needs because of glucocorticoids, and basal insulin will include 25%–40% of daily insulin needs.</li> </ul> <i>Challenges:</i> <ul style="list-style-type: none"> <li>• Patient ability to learn, self-monitor, and administer insulin can be a challenge.</li> <li>• Insulin dosing must be carefully managed and individualized depending on the severity of hyperglycemia, glucocorticoid dosing, and schedule.</li> <li>• Lack of insurance coverage can provide challenges.</li> <li>• The lack of availability of trained and knowledgeable providers for diabetic teaching can provide challenges.</li> <li>• The complexity of multiple insulin injections per day may deter providers and patients from choosing subcutaneous insulin.</li> <li>• For patients with anasarca, subcutaneous injections are not recommended; patients should be converted to an IV insulin drip.</li> </ul> <b>Oral antidiabetic agents</b><br><i>Benefits:</i> <ul style="list-style-type: none"> <li>• Oral product is easy for patients to take.</li> </ul> <i>Challenges:</i> <ul style="list-style-type: none"> <li>• Dose is difficult to adjust because of the long half-life.</li> <li>• Increased drug interactions exist.</li> <li>• The drug may be contraindicated in patients with renal dysfunction, edema, or cardiac disease.</li> <li>• Discontinuation of oral antidiabetic medications is recommended in glucocorticoid-induced hyperglycemia.</li> </ul> <i>Diet:</i> <ul style="list-style-type: none"> <li>• A carbohydrate-controlled diet is recommended.</li> <li>• Nutritional insulin is recommended if postprandial glucose is &gt; 180 mg/dl. The doses of insulin should be based on a carbohydrate/insulin ratio.</li> </ul> |

Note. Based on information from Brady et al., 2014; Clore & Thurby-Hay, 2009; Umpierrez et al., 2012.

From "Precursor Lymphoid Neoplasms," by C.M. Handy, M. Olsen, and L.J. Zitella, in M. Olsen and L.J. Zitella (Eds.), *Hematologic Malignancies in Adults* (p. 193), 2013, Oncology Nursing Society. Copyright 2013 by Oncology Nursing Society. Adapted with permission.

- (4) Manifestations
    - (a) Symptoms of hypothyroidism include fatigue, dry skin, cold sensitivity, constipation, depression, and weight gain.
    - (b) Manifestation (increased TSH and decreased free  $T_4$ ) can occur at any time but is usually six weeks after initiation of immune checkpoint inhibitors.
  - (5) Assessment: TSH and free  $T_4$  should be measured prior to treatment, at each treatment, four to six weeks after the final cycle, and every three months after that.
  - (6) Prevention and treatment: levothyroxine replacement at 1.6 mcg/kg daily
  - (7) Patient and family education
    - (a) Instruct patients and families to report symptoms of hypothyroidism.
    - (b) If thyroid hormone replacement has been initiated, instruct patients to take medication on an empty stomach in the morning.
- b) Hyperthyroidism (Barroso-Sousa et al., 2018; Hattersley et al., 2021; Spain et al., 2016)
- (1) Pathophysiology: Currently, no histopathologic findings exist. To date, a mechanism has not been established.
  - (2) Incidence: Hyperthyroidism occurs in 2.9%–8% of patients treated with immune checkpoint inhibitors (Hattersley et al., 2021).
  - (3) Risk factors
    - (a) Transient thyroiditis proceeding hypothyroidism
    - (b) TSH receptor antibody development
    - (c) Graves disease
  - (4) Manifestations: Symptoms usually occur 4–10 weeks after initiation of treatment and consist of weight changes, tachycardia, tremors, fatigue, diarrhea, and anxiety.
  - (5) Assessment
    - (a) Thyroid function testing should be performed prior to treatment, before each cycle for the first five cycles, four to six weeks after the final cycle, and every three months after that.
    - (b) If thyrotoxicosis is suspected, obtain TSH, free  $T_4$ , thyroid autoantibodies, cortisol, and glucose.
    - (c) With hyperthyroidism, a thyroid uptake scan may be clinically indicated to distinguish between Graves hyperthyroidism and thyroiditis.
- (6) Prevention and treatment
    - (a) Beta-blockers can be used to treat tremors, tachycardia, and other signs and symptoms of sympathetic activation.
    - (b) Methimazole may be used to treat Graves disease.
    - (c) For thyroiditis, the treatment is steroids. Steroids are not recommended if patients have low cardiovascular risk.
    - (d) If hypothyroidism results following prolonged hyperthyroidism, the treatment is levothyroxine 0.8–1.6 mcg/kg.
  - (7) Patient and family education
    - (a) Instruct patients and families to report symptoms, including palpitations, diarrhea, and tremors.
    - (b) If thyroid hormone replacement has been initiated, instruct patients to take medication on an empty stomach in the morning.
    - (c) Patients should be encouraged to carry an immunotherapy wallet card, indicating their diagnosis and immunotherapy (see Figure 10-3).
- c) Hypophysitis (González-Rodríguez & Rodríguez-Abreu, 2016; Sznol et al., 2017; Vazquez, 2017; Villadolid & Amin, 2015; Weber et al., 2015; Wright et al., 2021)
- (1) Pathophysiology: Hypophysitis may be caused by T-cell-mediated pituitary destruction due to CTLA-4 blockade.
  - (2) Incidence: The prevalence of hypophysitis is reported in up to 10% of patients treated with CTLA-4 inhibitors and 0.5%–1% of those treated with PD-1 and PD-L1 inhibitors.
  - (3) Risk factors: Male sex and older age
  - (4) Manifestations
    - (a) The most frequent complaints associated with hypophysitis are fatigue, headache, nausea, vomiting, and visual field defects, with magnetic resonance imaging showing swelling of the pituitary.
    - (b) Other manifestations include arthralgias, behavioral changes, and loss of libido.
    - (c) The usual time to the manifestation of symptoms is 9–12 weeks with ipilimumab and 26 weeks with PD-1 or PD-L1 inhibitors. These symptoms are likely permanent.

- (5) Assessment: A detailed history and physical examination should be performed prior to treatment. Each patient should have laboratory work completed consisting of the following:
    - (a) TSH
    - (b) Free T<sub>4</sub>
    - (c) Pituitary function tests (e.g., luteinizing hormone, follicle-stimulating hormone, growth hormone)
    - (d) Prolactin
    - (e) Adrenocorticotrophic hormone
    - (f) Cortisol
    - (g) Testosterone (in men)
    - (h) Estradiol (in women)
  - (6) Prevention: No preventive measures are reported.
  - (7) Treatment
    - (a) Corticosteroids should be used with caution for symptom control (Petrelli et al., 2020).
    - (b) For grade 3–4 adverse events, withhold treatment.
    - (c) If patients are asymptomatic, treatment measures include magnetic resonance imaging, hormone replacement, and cortisol replacement one week prior to the initiation of levothyroxine.
    - (d) If patients are symptomatic, recommendations include prednisolone (1–2 mg/kg), magnetic resonance imaging, and IV fluids for hypotension (if indicated). Steroids should be tapered over two to four weeks, followed by hormone replacement.
  - (8) Patient and family education
    - (a) Instruct patients and families to report any changes.
    - (b) Patients should be encouraged to carry an immunotherapy wallet card, indicating their diagnosis and immunotherapy (see Figure 10-3).
- d) Hyperglycemia (Hwangbo & Lee, 2017; Leiter et al., 2021)
- (1) Pathophysiology: PD-1, which is expressed on beta cells of islets (in the pancreas), is inhibited. Immune checkpoint inhibitors cause adipose tissue inflammation and lipodystrophy associated with insulin resistance.
  - (2) Incidence: Hyperglycemia occurred in 45%–49% of patients, with 3%–6% experiencing grade 3–4.
  - (3) Risk factors
    - (a) Underlying positive glutamic acid decarboxylase
    - (b) Human leukocyte antigen antibodies
    - (c) Low C-peptide (reference range: normal fasting C-peptide 1.1–4.4 ng/ml) (Kotwal et al., 2019)
    - (d) Asian or Hispanic ethnicity
    - (e) Obesity (body mass index greater than or equal to 30 kg/m<sup>2</sup>)
    - (f) Preexisting hyperglycemia
  - (4) Manifestations: Elevated blood glucose, which manifests in 0.4–107 weeks (median: 9.7 weeks) (Leiter et al., 2021)
  - (5) Assessment
    - (a) Check fasting blood glucose and hemoglobin A1c prior to initiation of treatment.
    - (b) Closely monitor blood glucose during treatment.
  - (6) Prevention and treatment
    - (a) Blood glucose should be adequately controlled using antidiabetic medications (oral agents or insulin) and adequate hydration.
    - (b) In the case of a sudden onset of severely elevated blood glucose, admission to a unit with a higher level of care (close monitoring) and administration of an insulin drip may be required.
  - (7) Patient and family education
    - (a) Depending on the severity of the blood glucose elevation, patients may need to learn how to perform self-monitoring of blood glucose and insulin injections.
    - (b) It may benefit patients and their families to attend a diabetes self-management education course.
    - (c) All patients should be educated on the signs and symptoms of hyperglycemia and instructed to report any symptoms related to diabetic ketoacidosis.
    - (d) Patients should be encouraged to carry an immunotherapy wallet card, indicating their diagnosis and immunotherapy.
- e) Diabetes (Alhousseini & Samantray, 2017; Barroso-Sousa et al., 2018; Fessas et al., 2020; Godwin et al., 2017; Kotwal et al., 2019; Nogueira et al., 2019; Paschou et al., 2021; Wright et al., 2021)
- (1) Pathophysiology: The pathophysiology includes destruction of pancreatic beta cells by autoreactive T cells.

- (2) Incidence: The incidence of type 1 diabetes was 0.4%–2% and associated with PD-1 and PD-L1 inhibitors (Barroso-Sousa et al., 2018; Higham et al., 2020; Kotwal et al., 2019; Nogueira et al., 2019; Paschou et al., 2021; Shariff et al., 2019; Wright et al., 2021).
- (3) Risk factors
  - (a) Previous history of prediabetes or diabetes
  - (b) Positive antibodies (e.g., glutamic acid decarboxylase, insulin autoantibodies, insulin antibodies)
  - (c) Asian ethnicity
  - (d) Obesity
  - (e) Older than age 60 years
  - (f) Human leukocyte antigen (HLA): Patients with HLA-DR3-DQ2 or HLA-DR4-DQ8 haplotypes appear to be at higher risk of developing immune checkpoint inhibitor-related type 1 diabetes (Barroso-Sousa et al., 2018).
- (4) Manifestations
  - (a) Elevation of blood glucose in people without a history of diabetes.
  - (b) Worsening of hyperglycemia in patients with a history of type 2 diabetes
  - (c) Onset: 1–228 weeks (median 7–17 weeks) after the first dose of an immune checkpoint inhibitor (Wright, et al., 2021)
- (5) Assessment: Blood glucose should be monitored every treatment cycle. For patients with new-onset hyperglycemia, a chemistry panel, urine ketones, serum ketones (beta-hydroxybutyrate), hemoglobin A1c, and C-peptide should be obtained.
- (6) Prevention and treatment
  - (a) Blood glucose and hemoglobin A1c should be monitored prior to treatment with immune checkpoint inhibitors. Blood glucose should be monitored with each treatment, and A1c should be obtained every three months (if patients have not received prior blood transfusions).
  - (b) Blood glucose should be adequately controlled using antidiabetic medications (oral agents or insulin) and adequate hydration.
  - (c) In the case of a sudden onset of severely elevated blood glucose, admission to a unit with a higher level of care (close monitoring) and administration of an insulin drip may be required.
  - (d) Referral to endocrinology is recommended.
- (7) Patient and family education
  - (a) Depending on the severity of the blood glucose elevations, patients may need to learn how to perform self-monitoring of blood glucose and insulin injections.
  - (b) It may also benefit patients and their families to attend a diabetes self-management education course.
  - (c) All patients should be educated on the signs and symptoms of hyperglycemia and instructed to report any symptoms related to diabetic ketoacidosis.
  - (d) Patients should be encouraged to carry an immunotherapy wallet card, indicating their diagnosis and immunotherapy (see Figure 10-3).
- f) Adrenal insufficiency (Barroso-Sousa et al., 2018; Dy & Adjei, 2013; Hattersley et al., 2021; Postow, 2022; Villadolid & Amin, 2015; Weber et al., 2015)
  - (1) Pathophysiology: Destruction of the adrenal cortex occurs, but the pathophysiology has not been fully elucidated.
  - (2) Incidence: Adrenal insufficiency occurs in less than 1% of patients and is more common among those treated with combination therapy (5%–7%) (Barroso-Sousa et al., 2018; Hattersley et al., 2021).
  - (3) Risk factors: Adrenal insufficiency was associated with the male sex.
  - (4) Manifestations: Symptoms usually occur within 10 weeks of initiation of treatment but can occur between 1–36 weeks.
    - (a) Dehydration
    - (b) Hypotension
    - (c) Electrolyte imbalances (e.g., hyperkalemia, hyponatremia)
    - (d) Abdominal pain and nausea
    - (e) Fever
    - (f) Hypoglycemia
    - (g) Fatigue
    - (h) Weakness
  - (5) Assessment
    - (a) Routine testing is not advised for patients treated with PD-1 or PD-L1 inhibitors. If symptoms occur, check thyroid hormones, serum glucose,



- electrolytes, adrenocorticotrophic hormone, and morning cortisol levels.
- (b) Perform magnetic resonance imaging of the pituitary gland within one month of diagnosis of adrenal insufficiency.
  - (c) Obtain an endocrinology consult.
- (6) Prevention and treatment
- (a) Hormone replacement therapy should be given if needed.
  - (b) Withhold treatment if evidence of an adrenal crisis.
  - (c) If severe symptoms of adrenal insufficiency are detected, patients should be hospitalized immediately and IV steroids initiated.
- (7) Patient and family education: Instruct patients and families to report signs and symptoms of the following:
- (a) Dehydration (e.g., dizziness, thirst, dry mouth, muscle fatigue)
  - (b) Hypotension (e.g., dizziness, lightheadedness, unsteadiness)
  - (c) Hyperkalemia (e.g., tachycardia, muscle weakness, muscle cramps, fatigue, chest pain)
  - (d) Hyponatremia (e.g., fatigue, nausea and vomiting, headache, confusion, muscle spasms)
- (8) If steroids are initiated, patients should learn the sick day rule for how to adjust steroids when ill (National Institutes of Health Clinical Center, 2016). Sick day rules for patients with adrenal insufficiency due to steroids outline the adjustment of the steroid dose when patients have an elevated temperature or vomiting and diarrhea.
- (9) Patients should wear medical alert necklaces or bracelets indicating that they have adrenal insufficiency.
- (10) Patients should be encouraged to carry an immunotherapy wallet card, indicating their diagnosis and immunotherapy.
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## CHAPTER 23

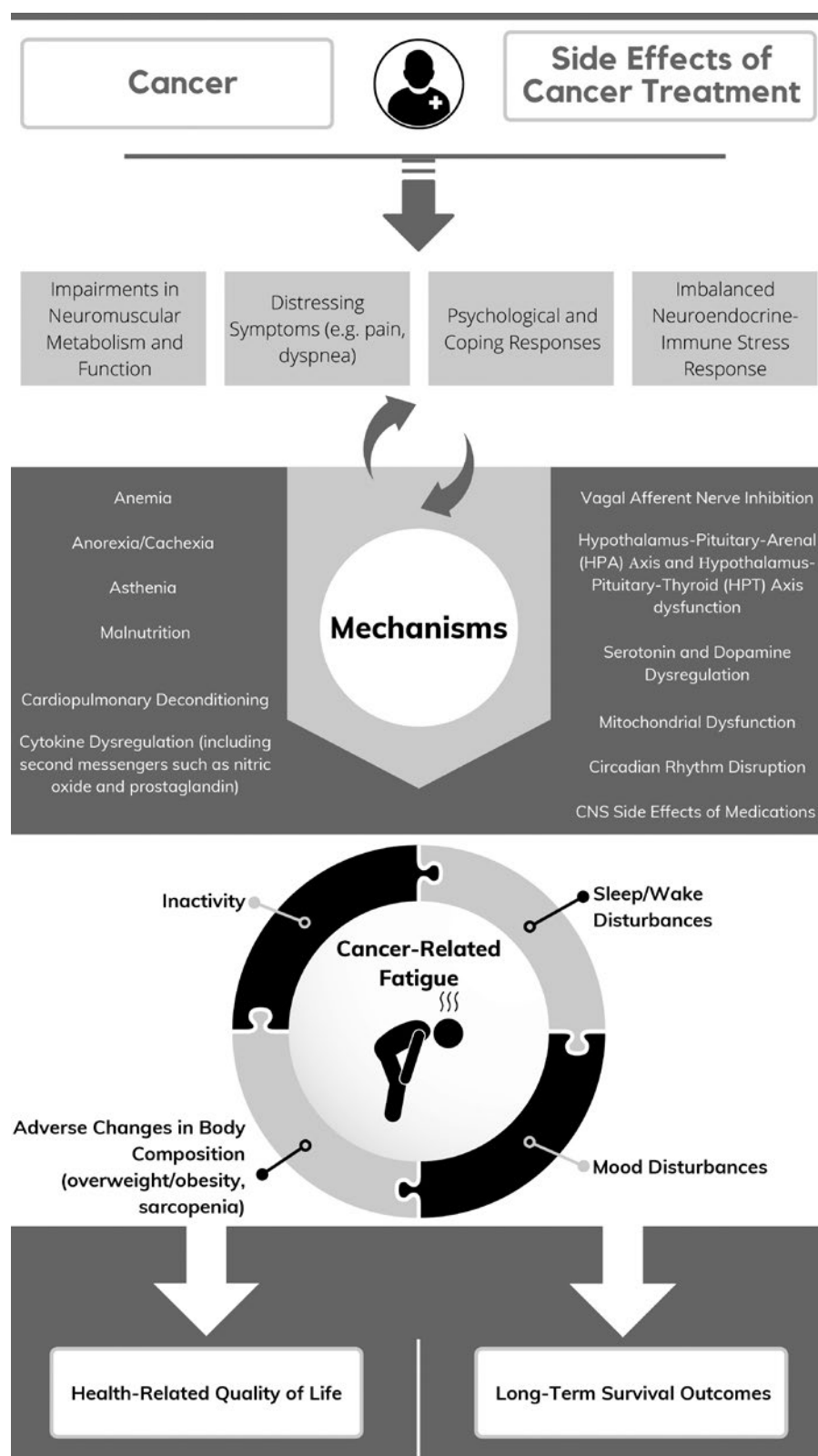
# Fatigue

### A. Overview

1. “Cancer-related fatigue is a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning” (National Comprehensive Cancer Network [NCCN], 2022, p. FT-1).
2. Multiple factors contribute to this complex syndrome in patients with cancer, making it challenging to identify a clear underlying cause (Bower, 2019; Gerber, 2017).
3. Cancer-related fatigue (CRF) is underreported, underdiagnosed, and undertreated. Healthcare professionals may not fully appreciate the degree of distress and functional loss that fatigue produces (Ripamonti et al., 2018; Thong et al., 2020). Fatigue is the most common, distressing, and disabling side effect of cancer treatment. It is also experienced by cancer survivors and those at the end of life (Charalambous et al., 2019; de Raaf, de Klerk, & van der Rijt, 2013).
4. It can produce profound decrements in physical, social, cognitive, and vocational functioning (Schmidt et al., 2020; Tan, Yip, et al., 2021), sleep disturbances (Charalambous et al., 2019), anxiety and depression (Brownstein et al., 2021; Ebede et al., 2017; Thompson & Bobonis Babilonia, 2017), and emotional and spiritual distress for patients and their family members (Bootsma et al., 2020; Miller et al., 2022; Schellekens et al., 2021).
5. NCCN guidelines recommend that all patients with cancer be screened for fatigue at their initial visit and at regular intervals across the cancer continuum. Fatigue in adults and children should be treated promptly (NCCN, 2022).

B. Pathophysiology: Exact mechanisms are unknown. Clinical studies have focused on understanding the factors contributing to CRF, including the tumor itself, treatments, late and long-term effects, and comorbid conditions (Ma et al., 2020).

1. Underlying mechanisms of CRF are believed to involve several physiologic and biochemical systems (Bower, 2019; Yang et al., 2019; see Figure 23-1).
  - a) Evidence suggests gene polymorphisms, hypothalamic-pituitary-adrenal disruption, altered circadian rhythmicity, diminished heart rate variability, immune dysfunction, serotonin dysregulation, mitochondrial dysfunction, 5-hydroxytryptophan dysregulation, and proinflammatory cytokine activity are mechanisms that directly or indirectly contribute to CRF.
  - b) Studies also suggest that fatigue may be related to impairments in neuromuscular metabolism and function, distressing symptoms such as pain and dyspnea, psychological and coping responses, and imbalanced neuroendocrine-immune stress responses (Brownstein et al., 2021; Chartogne et al., 2021; Feng et al., 2019; Hughes et al., 2020; Lacourt, Vichaya, Chiu, et al., 2018; Lacourt, Vichaya, Escalante, et al., 2018; Poort et al., 2017).
2. Direct effects of chemotherapies, hormone therapies, radiation therapies, molecularly targeted agents, immunotherapies, and combined-modality therapies have been implicated as contributors to the intensity of CRF (Abdel-Rahman et al., 2016; Li & Gu, 2017; Ma et al., 2020; Wagland et al., 2016). The burden of traveling to and from a clinic for treatments and office visits and the requirements for self-management during treatment can also amplify CRF.
3. The CRF disease process and comorbid conditions (e.g., metabolic disorders) can contribute to causing or exacerbating fatigue.
  - a) Endocrine dysfunction (e.g., hypothyroidism, adrenal insufficiency, testicular hypogonadism/androgen deficiency [low testosterone levels in males])
  - b) Cardiopulmonary dysfunction (e.g., cardiomyopathy, bronchiolitis, pneumonitis)
  - c) Dehydration and electrolyte imbalances
  - d) Infection

**FIGURE 23-1.** Etiology of Cancer-Related Fatigue

CNS—central nervous system

Note. Image courtesy Sandra A. Mitchell and Ann M. Berger. Used with permission.

- e) Insulin sensitivity: Insulin resistance causes abnormal glucose uptake by muscle and increases body fat, contributing to CRF (Yang et al., 2019).
  - f) Uncontrolled concurrent symptoms (e.g., pain, nausea and vomiting, dyspnea, anxiety)
  - g) Side effects of medications that act on the central nervous system (e.g., narcotics, anxiolytics, antiemetics)
  - h) Sleep disturbances (Charalambous et al., 2019; NCCN, 2022)
    - (1) Obstructive sleep apnea
    - (2) Restless legs syndrome/periodic limb movements
    - (3) Narcolepsy
    - (4) Insomnia (e.g., difficulty falling asleep, staying asleep, early morning awakening)
    - (5) Hypersomnia
  - i) Disease recurrence
  - j) Anemia: A relationship exists between low hemoglobin and fatigue. A decrease in red blood cells increases hypoxia-related compromise in organ function, contributing to fatigue (Kink et al., 2020).
  - k) Nutritional deficiencies: Reduced caloric intake and imbalances in serum levels of sodium, potassium, calcium, and magnesium may contribute to fatigue and affect quality of life (Inglis et al., 2019; NCCN, 2022).
  - l) Sarcopenia, physical deconditioning, and inactivity: Direct effects of the tumor or side effects of the treatment regimen often contribute to fatigue through sarcopenia (loss of muscle mass), reduced physical activity, cardiopulmonary deconditioning, and reduced muscle strength (Li, Chou, & Shun, 2021; Neefjes et al., 2017).
  - m) Psychological distress
  - n) Depression: Depression may occur concurrently with or independently of fatigue and can have a different pattern of expression over time (Bower, 2019; Müller et al., 2021).
  - o) Phenotypes/genotypes: Single nucleotide polymorphisms, especially in the regulatory regions of relevant genes, are thought to contribute to the development of CRF (Cameron et al., 2021; Wang et al., 2017).
- C. Incidence: Fatigue is one of the most reported symptoms experienced by patients receiving treatment for cancer, and it often persists beyond the conclusion of active treatment. Across the cancer care continuum, depending on how fatigue is defined and measured, prevalence estimates are 25%–99% (Christen et al., 2020; Ma et al., 2020; Thong et al., 2020).
- D. Assessment: Oncology nurses are responsible for ensuring that screening for CRF occurs and is documented at regular intervals across the cancer control continuum (Ebede et al., 2017; Pearson et al., 2016). A detailed evaluation of the characteristics, consequences, and potential contributing factors to fatigue should be performed, and fatigue should be managed with evidence-based interventions (NCCN, 2022).
1. Brief measures to screen for fatigue are rapid and sensitive and can be applied efficiently in the clinic to identify individuals who would benefit from additional systematic evaluation (Danjoux et al., 2007; Goedendorp et al., 2016; Kirsh et al., 2001; Temel et al., 2006).
  2. Increased availability of item banks, computerized adaptive testing, and collection and integration of patient-reported outcomes into the electronic health record may advance the precision, efficiency, interpretation, and actionability of screening measures for CRF (Lai et al., 2005, 2011; Wagner et al., 2015). Recent methodologies are exploring ways to combine self-report and performance-based assessments (Cuesta-Vargas et al., 2019), create interpretive crosswalks among various self-report measures of fatigue (Friedrich et al., 2019), and explore the role of sensors as digital biomarkers of fatigue (Sada et al., 2021).
  3. Multiple CRF screening and evaluation measures are available (Al Maqbali et al., 2019; Seyidova-Khoshknabi et al., 2011).
    - a) Single-item, single-dimension measures are easy to administer. These include a 0–10 scale, a visual analog scale, or Likert scales.
      - (1) On a 0–10 scale (0=no fatigue; 10=worst fatigue imaginable), mild fatigue is reflected by a score of 1–3, moderate by a score of 4–6, and severe by a score of 7–10 (NCCN, 2022).
      - (2) Fatigue measurement in children is simplified. Young children (aged younger than 6 years) may be asked if they are tired or not tired. Valid and reliable instruments are available to measure fatigue in children and adolescents (Christen et al., 2020; Tomlinson et al., 2013).
      - (3) If fatigue is absent or mild (score 0–3), patients and family members should receive anticipatory guidance about fatigue and available strategies for fatigue prevention and management (e.g., exercise, relaxation, stress management).
      - (4) When fatigue is rated as moderate to severe (4–10), a focused history and physical examination should be conducted as part of the primary evaluation phase.
    - b) More than 20 self-report measures, including single-item measures, multi-item unidimen-

sional scales, and multidimensional inventories, have been developed to evaluate fatigue in children, adolescents, and adults during and following cancer treatment (Al Maqbali et al., 2019; Christen et al., 2020; Seyidova-Khoshknabi et al., 2011; Tomlinson et al., 2013).

- (1) Consideration of the measurement properties and strengths and limitations of these instruments, including psychometric properties, sensitivity to change, and the availability of normative values to aid interpretation, combined with practical issues, such as respondent burden and availability of the measure in multiple languages, should guide decisions about the feasibility and usability of a measure for specific clinical or research purposes.
  - (2) Based on its sound psychometric properties, flexibility, and precision, the PROMIS (Patient-Reported Outcome Measurement Information System) instrument is recommended for fatigue measurement (Barsevick et al., 2013; Shaw et al., 2018). PROMIS measures are available for children (and parent proxies) and adults as short forms developed using item-response theory and as item banks for computerized adaptive testing.
4. NCCN (2022) guidelines recommend CRF assessment as a two-tiered approach. Patients should be screened for fatigue. Fatigue should be assessed quantitatively on a 0–10 scale if present. Patients who score 4 or higher should be further evaluated with a history and physical examination.
- a) A detailed history includes the presence, intensity, and pervasiveness of fatigue, its course over time, the factors that exacerbate or relieve fatigue, the effectiveness of the self-management interventions the patient has tried for fatigue, and the impact of fatigue on functioning and level of distress.
  - b) A complete review of systems should be performed.
  - c) Etiologic, potentiating, or predisposing factors that may contribute to CRF and which may be treatable should be evaluated. These factors include hypothyroidism, hypogonadism, adrenal insufficiency, cardiomyopathy, pulmonary dysfunction, anemia, neutropenia, cachexia, sleep disturbance, fluid and electrolyte imbalances, emotional distress, and uncontrolled concurrent symptoms (Alesi & del Fabbro, 2014; Berger et al., 2013; Bower, 2019; Koornstra et al., 2014; Kumar et al., 2018; Ma et al., 2020; Neeffes et al., 2013; Penson et al., 2021; Thong et al., 2020; Wang & Woodruff, 2014).

d) Evaluation should also include whether disease progression or recurrence could be among the causes of fatigue.

e) The medication profile should be reviewed to identify specific classes of medications that have fatigue as a potential side effect (e.g., over-the-counter medications). Polypharmacy is common in patients with cancer and has been associated with fatigue (Turner et al., 2016). Many drugs (e.g., antihistamines, beta-blockers) alone or in combination may significantly compound fatigue (Savard et al., 2015; Wang et al., 2014; Zlott & Byrne, 2010; see Table 23-1).

f) Other components of a comprehensive fatigue evaluation

- (1) Nutritional and metabolic evaluation: Improving dietary intake with appropriate caloric intake can often improve fatigue symptoms. Fluids and electrolytes should be assessed. Specifically, imbalances in sodium, potassium, calcium, and magnesium can be reversed with appropriate supplementation, which may improve fatigue (David et al., 2021; Inglis et al., 2019; NCCN, 2022).

- (2) Evaluation for symptoms such as nausea and vomiting, taste changes, bowel changes (e.g., obstruction, constipation, diarrhea), shortness of breath, pain, and sleep disturbances, individually or in symptom clusters, which may amplify fatigue (Charalambous et al., 2019; Kwekkeboom, 2016)

- (3) Physical activity level

#### E. Collaborative management

1. Treatable causes of fatigue should be screened for and managed, including concurrent distressing symptoms, physical deconditioning, endocrinopathies, emotional distress, and sedation secondary to specific medication classes.
  2. Across tumor types and at different places on the cancer continuum, the accumulated evidence strongly supports exercise as an intervention to manage CRF (Batalik et al., 2021; Capozzi et al., 2016, 2021; De Lazzari et al., 2021; Dun et al., 2020; Jiang et al., 2020; Kelley & Kelley, 2017; Nadler et al., 2019; NCCN, 2022; Song, Wang, Wang, Hong, et al., 2021; Vannorsdall et al., 2021; Wagoner et al., 2021).
- a) All patients with cancer should be encouraged to maintain an optimum level of physical activity during and following cancer treatment. Exercise improves aerobic capacity, prevents muscle loss and deconditioning, and may favorably affect sleep quality, psychological stress, mood, and

**TABLE 23-1.** Drug Classifications and Pharmacologic Agents Associated With Fatigue

| Drug Classification               | Examples                                                                                          | Potential Adverse Effects                     |
|-----------------------------------|---------------------------------------------------------------------------------------------------|-----------------------------------------------|
| Anticholinergics                  | Oxybutynin, tolterodine, trospium chloride                                                        | Fatigue, sedation                             |
| Anticonvulsants                   | Carbamazepine, gabapentin, pregabalin                                                             | Sedation, daytime sleepiness                  |
| Antidepressants                   | Paroxetine, sertraline                                                                            | Sedation, daytime sleepiness                  |
| Antiemetics                       | Haloperidol, metoclopramide, prochlorperazine, scopolamine                                        | Sedation, daytime sleepiness                  |
| Antihistamines                    | Diphenhydramine, hydroxyzine                                                                      | Sedation, daytime sleepiness                  |
| Anxiolytics, sedatives, hypnotics | Alprazolam, chloral hydrate, chlordiazepoxide, clonazepam, diazepam, doxepin, lorazepam, zolpidem | Sedation, daytime sleepiness                  |
| Barbiturates                      | Phenobarbital, secobarbital                                                                       | Sedation, daytime sleepiness                  |
| Beta-blockers                     | Atenolol, carvedilol, metoprolol                                                                  | Bradycardia                                   |
| Cannabinoids                      | Dronabinol, nabilone                                                                              | Sedation, daytime sleepiness                  |
| Corticosteroids                   | Dexamethasone, prednisone                                                                         | Sleep disturbances, proximal muscle weakness  |
| Hormone anticancer treatments     | Androgen deprivation therapy, aromatase inhibitors, selective estrogen receptor modulators        | Sarcopenia, fatigue, muscle weakness          |
| Opioid analgesics                 | Codeine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone                     | Sedation, daytime sleepiness                  |
| Skeletal muscle relaxants         | Baclofen                                                                                          | Sedation, daytime sleepiness, muscle weakness |

Note. Based on information from Savard et al., 2015; Wang et al., 2014; Zlott & Byrne, 2010.

- quality of life (Christensen et al., 2018; Nadler et al., 2019; Zyzniowska-Banaszak et al., 2021).
- b) Exercise may also favorably affect inflammation, the hypothalamic-pituitary-adrenal axis, circadian rhythm dysregulation, serotonin dysregulation, and alterations in adenosine triphosphate and muscle metabolism (Serdà i Ferrer et al., 2018).
  - c) Exercise intensity, frequency, and activity need further study to determine the most beneficial program for each individual and stage of disease (Sheill et al., 2018). Referral for structured rehabilitation may be helpful and is an effective intervention for CRF (Mitchell et al., 2014; NCCN, 2022).
  - d) National guidelines recommend that patients aim for at least 150 minutes of moderate-intensity physical activity (e.g., brisk walking, bicycling, swimming, deep water walking/running) each week and include strength training (all major muscle groups, 10 repetitions, 1–3 sets per exercise) twice weekly (Centers for Disease Control and Prevention, 2022).
  - e) Other types of physical activity can also be incorporated, including yoga, Pilates, tai chi, or organized sports.
  - f) Referrals to community-based exercise programs, comprehensive rehabilitation programs, or an exercise professional (e.g., physical therapist, exercise trainer, physiatrist) should be provided (Stout et al., 2019, 2021).
  - g) Although exercise programs are generally safe and well-tolerated across many types of cancer and stage along the continuum, these programs must be undertaken with caution and only after medical clearance, especially for patients with bone metastasis, immunosuppression, fever, thrombocytopenia, anemia, or peripheral neuropathy. Those at risk for falls or experiencing treatment complications should also proceed with caution (Schmitz et al., 2019, 2021). Models of care to support clinicians in providing physical activity recommendations to all patients during and following cancer treatment are beginning to emerge (Butts et al., 2021).
  - h) Medical clearance should be obtained prior to initiating an exercise program for patients with osteoporosis, bone metastases, neuropathy, neurologic disorders, weakness, cardiopulmonary dysfunction, arrhythmia, chest pain, shortness of breath, peripheral edema, or history of coronary



- artery disease. Compromised immunity requires clearance before using public gyms or pools. Patients with tunneled or peripherally inserted central venous catheters must avoid swimming.
- i) Programs should be initiated slowly to assess tolerance and can be modified or advanced as patient condition changes (NCCN, 2022). Walking, cycling, swimming, and resistance training have been evaluated and are appropriate modalities for patients. Programs that are too vigorous may increase fatigue.
  - j) Mobile health tools, such as activity monitors, smartphone applications, and social media websites, may strengthen motivation and adherence (Ester et al., 2021).
  - k) Relative contraindications to exercise include nonhealed surgical wounds, extreme fatigue, severe anemia, ataxia, and acute arm or shoulder problems (e.g., lymphedema [avoid upper body exercises]).
  - l) Patients should stop an exercise program and contact a member of the healthcare team if they experience dizziness, blurred vision, fainting, sudden onset of nausea or vomiting, unusual or sudden shortness of breath, irregular heart-beat, palpitations, chest pain, leg/calf pain, bone or joint pain, muscle cramping, or sudden onset of muscle weakness. During and in the period immediately following the conclusion of treatment, patients should be encouraged to exercise with a partner, caregiver, or exercise professional for safety reasons.
3. A meta-analysis of randomized controlled trials found yoga to be effective in reducing fatigue, particularly in breast cancer survivors (Dong et al., 2019; Hall et al., 2021; Lin et al., 2018; Liu et al., 2021; O'Neill et al., 2020; Song, Wang, Wang, Li, et al., 2021). However, systematic reviews have concluded that due to a high risk of bias in studies, the effectiveness of yoga on fatigue outcomes has not been sufficiently established as effective in reducing fatigue across a wide range of patient populations or at all points in the cancer continuum (Carlson et al., 2017).
  4. Tai chi and qigong have shown beneficial effects on fatigue outcomes in randomized clinical trials; however, study results should be interpreted cautiously due to heterogeneous study quality and high risk of bias (Hilfiker et al., 2018; Liu et al., 2021; Xiang et al., 2017; Yang et al., 2021; Zeng et al., 2014).
  5. Structured rehabilitation improves fatigue outcomes, particularly in cancer survivors (Hunter et al., 2017; Wirtz & Baumann, 2018). The rehabilitation interventions tested were generally multicomponent interventions that included exercise, psychoeducational support, mind-body therapies, and physical modalities (e.g., manual lymph drainage).
  6. Consistent evidence supports psychoeducational interventions to improve fatigue outcomes (Bennett et al., 2016; Hilfiker et al., 2018; Howell et al., 2017; Pearson et al., 2018; Poort et al., 2017; Ream et al., 2020; Sadeghi et al., 2016; Seiler et al., 2017; Tuominen et al., 2019).
    - a) Effective psychoeducational interventions include anticipatory guidance about patterns of fatigue, counseling and supportive psychotherapy, cognitive behavioral therapy (CBT), care coordination, and recommendations for energy conservation and self-management (e.g., exercise, lifestyle changes to improve sleep quality). The additions of coaching, praise, and encouragement augment feelings of control and promote self-efficacy.
    - b) CBT approaches (with or without hypnosis) for fatigue, depression, and pain are generally promising for the relief of CRF in patients with various cancers during and following treatment (Arring et al., 2019; Carlson et al., 2017; Cramer et al., 2015; David et al., 2021; Kwekkeboom, 2016; Kwekkeboom et al., 2018; Müller et al., 2021).
    - c) Energy conservation can balance rest and activity so that valued activities can be maintained (NCCN, 2022). This is a learned process for patients and is dictated by the disease experience.
      - (1) Instruct patients to delegate activities, pace themselves, take extra rest periods, plan high-energy activities at peak energy, and conserve energy for valued activities (NCCN, 2022).
      - (2) Recommend energy-saving devices (e.g., raised toilet seats, grabber tools, seated walkers, wheelchairs).
  7. Interventions designed to improve the management of concurrent symptoms (e.g., pain, depression, shortness of breath) have demonstrated an impact on fatigue outcomes. Evidence suggests that routine symptom monitoring alone, or in conjunction with an advanced practice registered nurse intervention and symptom-focused palliative and supportive care interventions, are efficacious approaches to manage CRF (de Raaf, de Klerk, Timman, et al., 2013; Kao et al., 2014; Klafke et al., 2019; Lizán et al., 2021; Yen-nurajalingam et al., 2011).
  8. CBT for insomnia to optimize sleep quality has decreased CRF (Dun et al., 2021; NCCN, 2022).
    - a) This intervention can be delivered individually, in a group setting, or via the internet (Büttner-Teleagă et al., 2021).
    - b) CBT for insomnia may take several weeks of steady practice to become fully effective and

usually requires four to eight 30-minute sessions with a behavioral sleep therapist, such as a nurse, psychologist, or other professional.

c) Components of CBT for insomnia

- (1) Stimulus control: Go to bed only when sleepy, use bed/bedroom for sleep and sexual activities only, and maintain a consistent presleep routine and time to lie down and get up.
  - (2) Sleep consolidation: Limit the amount of time in bed, including naps.
  - (3) Sleep hygiene: Avoid caffeine late in the day and provide a comfortable sleep environment to promote a good night's sleep.
  - (4) Intervention components also include relaxation training and strategies to reduce cognitive emotional arousal (e.g., reserving at least an hour to relax before bed, establishing a presleep routine).
9. Meditation, mindfulness-based stress reduction, and cognitive behavioral stress management, including internet-based interventions, can improve fatigue severity and fatigue-related daytime interference during and following cancer treatment (David et al., 2021; Haller et al., 2017; He et al., 2020; NCCN, 2022; Schell et al., 2019; Toivonen et al., 2017; Wyatt et al., 2021; Xie et al., 2020; Zhang et al., 2019).
  10. Progressive muscle relaxation with or without imagery, relaxation breathing, coping skills training, and distraction delivered in a series of sessions have demonstrated effectiveness in improving fatigue outcomes (Carlson et al., 2017; Hilfiker et al., 2018).
  11. Bright-light therapy has been shown in several controlled trials to prevent deterioration in CRF during treatment (Hung et al., 2021; Xiao et al., 2022) and in cancer survivors after treatment (Johnson et al., 2018). The underlying mechanism of action remains an area of active research and may include protecting recipients from circadian rhythm desynchronization (Johnson et al., 2020) and improving depression (Kronish et al., 2020). Trials of this promising therapy are ongoing and employing more rigorous and reproducible study designs.
  12. Evidence for the effectiveness of acupuncture, acupressure, self-acupuncture, and electroacupuncture in reducing CRF has been summarized in nearly a dozen meta-analyses and systematic reviews (Arring et al., 2019; Han et al., 2021; Hsieh et al., 2021; Jang et al., 2020; Tan, Wang, et al., 2021; Wu et al., 2019; Zhang et al., 2018). Although most of these reviews concluded that acupuncture and acupressure interventions are beneficial, acceptable, and well-tolerated, the authors drew somewhat conflicting conclusions about whether these interventions were ready for translation into practice. All have urged additional studies using rigorous trial designs.
  13. Complementary and integrative therapies, including polarity therapy (energy therapy), moxibustion (heat therapy), healing touch, Reiki, reflexology, and massage, may improve CRF (Ben-Arye et al., 2018; Carlson et al., 2017; David et al., 2021; Hilfiker et al., 2018; Mao et al., 2016; Wang et al., 2021; Wyatt et al., 2021). Continued study of these potentially promising interventions with longer follow-up and active control conditions is warranted. Complementary and integrative medicine strategies are well-tolerated and may be particularly useful when other methods are contraindicated or infeasible. They can also be considered to augment different treatment approaches for fatigue, such as yoga, relaxation, or CBT.
  14. Because the exact pathophysiology of CRF is obscure and multifactorial, pharmacotherapy is empiric or geared toward reversing possible contributing factors, such as anemia, poor nutrition, or depression (Belloni et al., 2021; Chow et al., 2021; Inglis et al., 2019; Klasson et al., 2021; Sun et al., 2021).
    - a) Although data from several systematic reviews suggest that patients receiving recombinant human erythropoietin to correct anemia less than 10 g/dl may experience increased vigor and diminished fatigue, only limited evidence suggests erythropoiesis-stimulating agents improve fatigue when anemia is less severe (Bohlius et al., 2019). Importantly, erythropoiesis-stimulating agents to manage fatigue cannot be recommended because of safety issues (Aapro et al., 2018; Schoen et al., 2020). National clinical practice guidelines should weigh risks and benefits and guide the management of patients receiving these agents (Bohlius et al., 2019; Gawade et al., 2017; NCCN, 2021).
    - b) Antidepressants have been recommended to treat fatigue, particularly when depression is suggested as a causal factor. Although drugs such as paroxetine, bupropion, and venlafaxine may help alleviate depression, studies have not consistently demonstrated a clinically significant benefit to their use compared to placebo in nondepressed patients with fatigue, and they are not explicitly recommended to lessen fatigue (Chow et al., 2021; Klasson et al., 2021; Mitchell et al., 2014; Mücke et al., 2016; NCCN, 2022; Sun et al., 2021). Small trials have shown a trend toward a possible benefit for antidepressant agents in treating fatigue in women experiencing hot flashes and patients receiving interferon alpha.

- c) Several systematic reviews produced preliminary evidence suggesting that psychostimulants (e.g., methylphenidate, dexamethylphenidate, modafinil) may help treat fatigue (Belloni et al., 2021; Qu et al., 2016; Sun et al., 2021). However, given the mixed evidence for efficacy and concern about the potential for side effects (e.g., headache, insomnia, agitation, anorexia, nausea, vomiting, dry mouth), the use of these agents outside the context of a clinical trial has been discouraged (Barton, 2014; Ruddy et al., 2014).
- d) Corticosteroids (e.g., prednisone, dexamethasone) have short-term efficacy in ameliorating CRF. Given the potentially detrimental side effects of muscle wasting and infection with long-term use, it is difficult to draw definitive conclusions about their risk–benefit profile (Klasson et al., 2021).
- e) Megestrol acetate is widely used for appetite improvement, and its safety and efficacy have been confirmed in treating cancer cachexia. However, a meta-analysis of the four trials that compared progestational steroids with placebo found no difference in the two arms for reducing CRF (NCCN, 2022; Payne et al., 2012).
- f) Although male hypogonadism is thought to be a contributor to fatigue (Vigano et al., 2010), a blinded, placebo-controlled trial of testosterone replacement in a small sample of men with advanced cancer did not improve fatigue end points (Del Fabbro et al., 2013).
- g) Thyrotropin-release hormone improved fatigue outcomes in a small, randomized, placebo-controlled crossover pilot study in eight patients with cancer and significant fatigue (Kamath et al., 2012).
- h) Targeted anticytokine therapy (e.g., etanercept, infliximab) may have favorable effects on CRF (Monk et al., 2006; Tookman et al., 2008); however, small sample sizes and the use of nonrandomized study designs that limit the strength of the conclusions that can be drawn about the efficacy of these therapies in treating CRF.
- i) Wisconsin, Asian, and fermented red ginseng extract have effectively improved fatigue outcomes in patients during and following cancer treatment (Arring et al., 2018, 2019; Inglis et al., 2019). The optimal dose and duration of these treatments are unknown (Lemke, 2021). Possible drug–drug interactions must also be considered (Choi & Song, 2019).
- j) Several nutritional and herbal supplements (e.g., guarana, essiac, valerian, vitamin supplements, zinc, levocarnitine, coenzyme Q10,

mistletoe extract, melatonin) and combined modality interventions that incorporate several complementary therapies (e.g., megestrol acetate, omega-3 fatty acid supplementation) have been evaluated with mixed evidence for efficacy (Inglis et al., 2019; Marx et al., 2017; NCCN, 2022; Sun et al., 2021). Interpretation of the study outcomes in these trials is limited by small sample sizes and the predominant use of single-arm, open-label study designs (Klasson et al., 2021).

#### F. Principles of patient and family education and care planning

1. Management of fatigue originates with the primary oncology team assessing fatigue as a symptom related to treatment and disease status. Begin with an initial screening and expand to a more focused evaluation for moderate and higher levels of fatigue (NCCN, 2022).
2. Inform patients and family members that fatigue is a significant symptom of the disease and the treatment process. Patterns are variable and do not necessarily indicate treatment failure or disease progression. Discuss multifactorial causes of fatigue, including psychosocial stressors, concurrent symptoms, sleep disturbances, muscle weakness and deconditioning, sedating side effects of medications, and proinflammatory cytokine release. Clarify effective interventions to manage fatigue and create an individualized and multicomponent treatment plan (Lacourt et al., 2020; Martin et al., 2021).
3. Daily self-monitoring of fatigue levels in a log or diary can be helpful (NCCN, 2022). Encourage patients to differentiate facets of the fatigue experience (e.g., fatigue, tiredness, weakness, cognitive slowing) and document the use and effectiveness of self-management interventions (e.g., exercise, sleep, progressive muscle relaxation, meditation).
4. Offer anticipatory guidance about possible patterns of when fatigue may develop or worsen, including at the time of white blood cell nadir, when radiation therapy concludes, and in association with demanding physical activity, impairments in sleep quality, psychological stress, and concurrent symptoms.
5. Develop and tailor an individualized plan for fatigue management that considers factors that may influence specific fatigue management interventions (Charles et al., 2021).
6. Inform patients and family that interventions such as energy conservation, exercise, relaxation and stress management, psychosocial support, and measures to optimize sleep quality and reduce concurrent symptoms can be effective in limiting the severity of fatigue during treatment.

7. Teach energy conservation strategies and other fatigue self-management techniques. Provide coaching to enhance self-efficacy for fatigue management and discern ways to integrate these techniques into daily life.
8. Provide information concerning the importance of a balanced diet with adequate intake of fluid, calories, protein, carbohydrates, fat, vitamins, and minerals (NCCN, 2022).
9. Instruct patients about implementing a balanced exercise program (e.g., walking, stretching, strength training). Encourage patients to continue normal activities and to remain as active as possible during treatment. Following treatment, the exercise program should be advanced as tolerated, gradually building up the length and intensity of physical activity to meet national guidelines of at least 150 minutes of moderate-intensity physical activity each week. Offer referrals to exercise professionals and community-based exercise programs.
10. Offer information and referrals to counseling or a support group (in person or online). Supportive expressive therapies, counseling, and journal writing may serve as emotional outlets and avenues for support and encouragement (NCCN, 2022). Oncology nurses frequently provide this one-on-one education and support for the patient.
11. Care planning
  - a) Causes of CRF are often overlapping and may evolve across the cancer continuum from diagnosis to treatment to survivorship or end of life. Therefore, intervention approaches are symptom oriented and individualized (Chartogne et al., 2021).
  - b) The care plan should be regularly revised based on goals, preferences, response, and tolerance.
  - c) A multimodal approach that includes exercise, psychoeducational interventions, management of concurrent symptoms, and efforts to improve sleep quality, combined with judicious use of complementary therapies, such as relaxation, massage, acupuncture, or bright light therapy, offers the greatest likelihood of success and is consistent with evidence-based guidelines from the Oncology Nursing Society (Mitchell et al., 2014), International Late Effects of Childhood Cancer Guideline Harmonization Group (Christen et al., 2020), American Society of Clinical Oncology (Bower et al., 2014), and NCCN (2022).
  - d) Consideration may be given to a trial of antidepressants, psychostimulants, wakefulness-promoting agents, corticosteroids, or ginseng in specific clinical circumstances.

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## CHAPTER 24

# Neurologic Toxicities

### A. Overview

1. *Neurotoxicity* refers to an injury to the brain and spinal cord (central nervous system [CNS]) or the peripheral nervous system (nervous system outside of the brain and spinal cord) caused by exposure to natural or manufactured toxic substances.
2. Cancer therapies can induce a range of toxic side effects (see Table 24-1) on nervous tissue, resulting in significant morbidity and mortality, which may persist beyond the treatment period.
3. Neurologic toxicity from cancer therapies is a common problem for patients and second only to myelosuppression as a root cause of dose modification or discontinuation (Dietrich, 2020).
4. Besides this potential to limit the overall efficacy of the cancer treatment, neurologic sequelae have become some of the most important challenges in patient survivorship (Wick et al., 2016).
5. Neurotoxicity presents most frequently as fatigue and peripheral neuropathies (see Table 24-2), although many clinical symptoms have been reported.
6. Acute toxicities (e.g., seizure), encephalopathy, and cerebrovascular events (e.g., thromboembolic stroke, hemorrhage) require immediate intervention.
7. Therefore, oncology nurses must regularly assess for and recognize early neurotoxicity to allow for rapid diagnosis, treatment, and dose adjustment to mitigate the risk of irreversible neurologic impairment.

### B. Radiation-induced CNS toxicity

1. Neurotoxicity is often the result of the synergistic effects of concurrent chemotherapy and radiation.
2. General neurotoxicities
  - a) Overview
    - (1) Direct or ancillary exposure of nervous tissue to radiation therapy carries a risk of neurologic injury.
    - (2) General neurotoxicities result from permeating injury to brain tissue with accompanying nonspecific symptoms,

such as headache, fatigue, and nausea (Rahman et al., 2020; Tanguturi & Alexander, 2018).

#### b) Pathophysiology

- (1) Radiation delivered to the entire brain (i.e., whole-brain radiation therapy), partial brain radiation therapy, or targeted radiation therapy (e.g., stereotactic radiosurgery, Gamma Knife®) causes irreversible injury to brain tissue that frequently results in the death of healthy brain tissue as well as tumor tissue (Ai et al., 2020).
- (2) Swelling of the brain and meninges following radiation can further potentiate injury, and this edema often is the root cause of acute neurotoxicity. Delayed neurotoxicities are frequently attributed to demyelination or vasculopathy (Stubblefield, 2017b).

#### c) Incidence

- (1) Radiation therapy is often synergistic with chemotherapy but carries an independent risk of neurotoxicity.
- (2) Incidence and severity vary according to multiple factors, including radiation dose and type, treatment sites, and body mass index.

#### d) Clinical manifestations

- (1) Neurologic sequelae often are described temporally to the administration of radiation therapy as acute (during or immediately after treatment), early-delayed (weeks to months following treatment), and late-delayed (months to years following treatment) (Rahman et al., 2020; Schiller et al., 2017).
- (2) Acute through early-delayed symptoms are generally reversible and include headache, fatigue, nausea, irritability, somnolence, and encephalopathy. They may be associ-

**TABLE 24-1.** Central Neurotoxicity in Chemotherapy, Immunotherapy, and Targeted Therapies

| Adverse Effect                                                                           | Signs and Symptoms                                                                                                                                                       | Reported Agents                                                                                                                                                                                                                                                                                                                                                                                                     | Potential Treatment                                                                                                                                                                                |
|------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Aseptic meningitis                                                                       | Fever<br>Headache<br>Nausea/vomiting<br>Photophobia<br>Protein, white blood cells in cerebrospinal fluid<br>Stiff neck                                                   | Cetuximab<br>Cytarabine (high dose)<br>Ipilimumab<br>IV immunoglobulin<br>Methotrexate<br>Rituximab                                                                                                                                                                                                                                                                                                                 | Consider analgesics, antiemetics, or IV fluids.<br>Discontinue drug.<br>Initiate steroids.                                                                                                         |
| Cerebellar syndrome                                                                      | Altered mental status<br>Ataxia<br>Dizziness<br>Dysarthria<br>Dysmetria<br>Dysphagia<br>Gait imbalance<br>Nystagmus<br>Uncoordinated movements                           | Altretamine<br>Bortezomib<br>Capecitabine<br>Cytarabine<br>5-Fluorouracil<br>Nelarabine<br>Oxaliplatin<br>Procarbazine<br>Rituximab<br>Thalidomide<br>Trastuzumab<br>Vincristine                                                                                                                                                                                                                                    | Discontinue drug.                                                                                                                                                                                  |
| Cerebrovascular events (e.g., thromboembolism, intracranial hemorrhage, ischemic stroke) | Altered mental status<br>Decreased alertness<br>Difficulty speaking<br>Headache<br>Loss of consciousness<br>Nausea/vomiting<br>Neurologic deficit<br>Seizure<br>Weakness | Bevacizumab<br>Cisplatin<br>Cyclosporine<br>Doxorubicin<br>Estramustine<br>L-Asparaginase<br>Lenvatinib<br>Methotrexate<br>Osimertinib<br>Ramucirumab<br>Sorafenib<br>Sunitinib<br>Thalidomide<br>Vandetanib                                                                                                                                                                                                        | Consider analgesics, anticoagulation therapies, antiepileptics, platelet inhibitors, thrombolytics, steroids, or surgical intervention.<br>Replace electrolytes.<br>Pause or discontinue the drug. |
| Encephalopathy (acute and chronic)                                                       | Agitation<br>Cerebellar ataxia<br>Cognitive dysfunction<br>Confusion<br>Disorientation<br>Lethargy<br>Loss of consciousness<br>Seizure                                   | Altretamine<br>Atezolizumab<br>Avelumab<br>Axicabtagene ciloleucel<br>Azacitidine<br>Blinatumomab<br>Bortezomib<br>Busulfan<br>Carmustine<br>Cemiplimab-rwlc<br>Chimeric antigen receptor T cells<br>Cisplatin<br>Cyclophosphamide<br>Cytarabine<br>Dacarbazine<br>Docetaxel<br>Doxorubicin<br>Durvalumab<br>Etoposide<br>Fludarabine<br>5-Fluorouracil<br>Gemcitabine<br>Ifosfamide<br>Imatinib<br>Interferon alfa | Implement drug interruption with steroid course or discontinue the drug.<br>Consider rituximab for autoimmune encephalitis if there is no improvement with steroids.                               |

(Continued on next page)

**TABLE 24-1.** Central Neurotoxicity in Chemotherapy, Immunotherapy, and Targeted Therapies (*Continued*)

| Adverse Effect                                         | Signs and Symptoms                                                    | Reported Agents                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Potential Treatment                                                                                          |
|--------------------------------------------------------|-----------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|
| Encephalopathy (acute and chronic)<br>( <i>Cont.</i> ) |                                                                       | Interleukin-2<br>Ipilimumab<br>L-Asparaginase<br>Methotrexate (high dose)<br>Mitomycin C<br>Nelarabine<br>Nitrosoureas<br>Nivolumab<br>Paclitaxel<br>Pembrolizumab<br>Procarbazine<br>Tamoxifen<br>Thalidomide<br>Thiotepa<br>Vincristine                                                                                                                                                                                                                          |                                                                                                              |
| Headache                                               | Pain<br>Pressure                                                      | Altretamine<br>Bevacizumab<br>Cetuximab<br>Chimeric antigen receptor T cells<br>Crizotinib<br>Dabrafenib<br>Dasatinib<br>Etoposide<br>5-Fluorouracil<br>Fludarabine<br>Hexamethylamine<br>Imatinib<br>Intrathecal chemotherapy: any drug<br>Ipilimumab<br>Ixabepilone<br>Larotrectinib<br>L-Asparaginase<br>Mechlorethamine<br>Methotrexate<br>Nelarabine<br>Procarbazine<br>Retinoic acid<br>Rituximab<br>Tamoxifen<br>Temozolomide<br>Trastuzumab<br>Vemurafenib | Discontinue drug.<br>Consider analgesics.<br>Consider hormone replacement or steroids depending on etiology. |
| Hypophysitis                                           | Fatigue<br>Headache<br>Visual disturbances                            | Atezolizumab<br>Avelumab<br>Cemiplimab<br>Durvalumab<br>Ipilimumab<br>Nivolumab<br>Pembrolizumab                                                                                                                                                                                                                                                                                                                                                                   | Discontinue drug.<br>Initiate steroids.<br>Consider hormone replacement.                                     |
| Myelopathy                                             | Back pain<br>Incontinence of bowel or bladder<br>Numbness<br>Weakness | Cytarabine<br>Methotrexate<br>Thiotepa                                                                                                                                                                                                                                                                                                                                                                                                                             | Discontinue drug.<br>Initiate steroids.                                                                      |

(Continued on next page)

**TABLE 24-1.** Central Neurotoxicity in Chemotherapy, Immunotherapy, and Targeted Therapies (*Continued*)

| Adverse Effect                               | Signs and Symptoms                                                                                                                                                                                     | Reported Agents                                                                                                                                                                                                                                                                                                                                                 | Potential Treatment                                                                              |
|----------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Ototoxicity                                  | Hearing loss<br>Tinnitus                                                                                                                                                                               | Carboplatin<br>Carmustine<br>Cisplatin<br>Oxaliplatin<br>Vincristine                                                                                                                                                                                                                                                                                            | Discontinue drug.                                                                                |
| Posterior reversible encephalopathy syndrome | Altered mental status<br>Confusion<br>Headache<br>Hypertension<br>Lethargy<br>Nausea<br>Seizure<br>Somnolence<br>Visual disturbances<br>Vomiting                                                       | Axitinib<br>Bevacizumab<br>Capecitabine<br>Carboplatin<br>Cisplatin<br>Cyclophosphamide<br>Cyclosporine<br>Cytosine arabinoside<br>5-Fluorouracil<br>Gemcitabine<br>Ifosfamide<br>Imatinib<br>Methotrexate (high dose)<br>Nelarabine<br>Pazopanib<br>Ramucirumab<br>Rituximab<br>Sirolimus<br>Sorafenib<br>Sunitinib<br>Tacrolimus<br>Vandetanib<br>Vincristine | Discontinue drug.<br>Stabilize blood pressure.<br>Consider antiepileptic therapy or prophylaxis. |
| Progressive multifocal leukoencephalopathy   | Altered mental status (confusion)<br>Aphasia<br>Ataxia<br>Dysarthria<br>Dysmetria<br>Headache<br>Hemiparesis<br>Neglect<br>Parkinsonism<br>Seizure<br>Sensory deficits<br>Vertigo<br>Visual impairment | Alemtuzumab<br>Bevacizumab<br>Brentuximab<br>Carmustine<br>Cetuximab<br>Cytarabine<br>Fludarabine<br>Ibritumomab<br>Ibrutinib<br>Idelalisib<br>Ifosfamide<br>Infliximab<br>Methotrexate (high dose)<br>Ofatumumab<br>Rituximab<br>Thalidomide<br>Vincristine                                                                                                    | Discontinue drug.<br>Initiate steroids.                                                          |
| Seizures                                     | Altered mental status<br>Involuntary jerking<br>Loss of consciousness<br>Staring spells<br>Temporary confusion<br>Violent movements of arms/legs                                                       | Amsacrine<br>Axicabtagene ciloleucel<br>Brexucabtagene autoleucel<br>Busulfan (high dose)<br>Carmustine<br>Chlorambucil<br>Cisplatin<br>Cyclosporine<br>Cytarabine (high dose)<br>Dacarbazine<br>Etoposide<br>5-Fluorouracil                                                                                                                                    | Antiepileptics<br>Replace electrolytes.<br>Pause or discontinue drug.                            |

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**TABLE 24-1.** Central Neurotoxicity in Chemotherapy, Immunotherapy, and Targeted Therapies (*Continued*)

| Adverse Effect               | Signs and Symptoms | Reported Agents                                                                                                                                                                                                                                                                                                                | Potential Treatment |
|------------------------------|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|
| Seizures<br>( <i>Cont.</i> ) |                    | Fludarabine<br>Gemcitabine<br>Idecabtagene vicleucel<br>Ifosfamide<br>Intrathecal chemotherapy: any drug<br>L-Asparaginase<br>Lisocabtagene maraleucel<br>Lorlatinib<br>Methotrexate (high dose)<br>Naxitamab-gqgk<br>Nelarabine<br>Nitrosoureas<br>Paclitaxel<br>Teniposide<br>Thalidomide<br>Tisagenlecleucel<br>Vincristine |                     |

Note. Based on information from AstraZeneca Pharmaceuticals, 2021; Bayer HealthCare Pharmaceuticals, 2021; Bristol-Myers Squibb, 2021b, 2021c; Cintrón-García & Guddati, 2020; Dietrich, 2020; EMD Serono, 2021; Genentech, 2021; Haugh et al., 2020; Juno Therapeutics, 2021; Kite Pharma, 2021a, 2021b; Merck, 2021; Novartis Pharmaceuticals, 2021; Pfizer, 2021a, 2021b; Pinner & Tierney, 2020; Regeneron Pharmaceuticals, 2021; Stone & DeAngelis, 2016; Wick et al., 2016; Y-mAbs Therapeutics, 2020; Zukas & Schiff, 2018.

ated with fever, vomiting, drowsiness, and exacerbation of focal deficits (Rahman et al., 2020; Smart, 2017; Tanguturi & Alexander, 2018).

- (3) Delayed neurotoxicity from radiation therapy is usually progressive and irreversible. Sequelae can include leukoencephalopathy, necrosis, cystic degeneration, hydrocephalus, cerebrovascular events such as infarct or hemorrhage, radiation-induced tumors, parenchymal calcifications, brain atrophy, and cognitive impairment (Rahman et al., 2020; Turnquist et al., 2020).

e) Assessment

- (1) Diagnosis is typically by patient self-report of symptoms.
- (2) Careful neurologic assessment may reveal focal deficits or altered mental status and encephalopathy.
- (3) Leukoencephalopathy, cystic degeneration, hydrocephalus, cerebrovascular events, second tumors, and parenchymal calcifications are usually seen radiographically; however, a surgical biopsy may be required to achieve the final diagnosis.

f) Collaborative management

- (1) Limited literature shows promising evidence for using lithium as a prophylactic measure to prevent radiation-induced cell death (Turnquist et al., 2020).

- (2) Treatment for acute toxicity includes careful planning and directed pharmacologic intervention (e.g., steroids for swelling, antiemetics for nausea and vomiting).

- (3) For delayed toxicities, preliminary evidence in animal studies supports using renin-angiotensin system blockers to decrease the inflammatory process and subsequent cell injury induced by radiation therapy (Turnquist et al., 2020).

- (4) Other late toxicities often require surgical intervention, such as hydrocephalus, cerebrovascular events, and the development of radiation-induced tumors.

- (5) For other types (e.g., brain atrophy, cognitive impairment, parenchymal calcifications), no treatment options may be available.

3. SMART syndrome (stroke-like migraine attacks after radiation therapy)

- a) Overview: SMART syndrome is a delayed neurotoxic effect occurring anywhere from 1 to 37 years following radiation treatment to the brain (Dominguez & Malani, 2021; Singh et al., 2017).

b) Pathophysiology

- (1) The etiology is uncertain, but conflicting evidence suggests SMART syndrome is caused by neuronal dysfunction or cerebral vascular pathology (Singh et al., 2017).



**TABLE 24-2.** Peripheral Neuropathy<sup>a,b</sup>

| Classification                 | Agents                                                                                                                                | Type of Neuropathy                          | Symptoms                                                                                                                                                                                                                                               |
|--------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Alkylating Agents</b>       |                                                                                                                                       |                                             |                                                                                                                                                                                                                                                        |
| Hydrazines and triazines       | Altretamine<br>Procarbazine                                                                                                           | Sensory                                     | Myalgia<br>Paresthesias                                                                                                                                                                                                                                |
| Platinum-based agents          | Carboplatin<br>Cisplatin<br>Oxaliplatin                                                                                               | Sensory                                     | Ataxia<br>Coasting phenomenon <sup>c</sup><br>Cold-induced neuropathy<br>Hearing loss<br>Jaw spasm<br>Lhermitte syndrome<br>Muscle cramps<br>Numbness<br>Paresthesias<br>Reduced deep tendon reflexes (DTR)<br>Sense vibration<br>Tingling<br>Tinnitus |
| <b>Plant Alkaloids</b>         |                                                                                                                                       |                                             |                                                                                                                                                                                                                                                        |
| Antimetabolites                | Azacitidine<br>Capecitabine<br>Cladribine<br>Cytarabine<br>Fludarabine<br>5-Fluorouracil<br>Gemcitabine<br>Methotrexate<br>Nelarabine | Sensory                                     | Ataxia<br>Brachial plexopathy<br>Disorientation<br>Dysarthria<br>Hallucinations<br>Myopathy<br>Paresthesias<br>Seizures                                                                                                                                |
| Taxanes                        | Cabazitaxel<br>Docetaxel<br>Nab-paclitaxel<br>Paclitaxel                                                                              | Autonomic<br>Motor<br>Sensory               | Arrhythmia<br>Dysesthesias<br>Impaired/lost sensation<br>Neuropathic pain<br>Optic neuropathy<br>Orthostatic hypotension<br>Paresthesias<br>Reduced/lost DTR<br>Weakness                                                                               |
| Vinca alkaloids                | Vinblastine<br>Vincristine<br>Vindesine<br>Vinflunine<br>Vinorelbine                                                                  | Autonomic<br>Cranial nerves<br>Sensorimotor | Coasting phenomenon<br>Constipation<br>Foot drop<br>Lower limb weakness<br>Muscle cramps<br>Myopathy<br>Neuropathic pain<br>Orthostatic hypotension<br>Paralytic ileus<br>Paresthesias<br>Reduced/lost DTR<br>Sensory impairment                       |
| <b>Targeted Therapy Agents</b> |                                                                                                                                       |                                             |                                                                                                                                                                                                                                                        |
| Monoclonal antibodies          | Alemtuzumab<br>Bevacizumab<br>Brentuximab<br>Ibritumomab<br>Ipilimumab<br>Pertuzumab<br>Rituximab                                     | Sensorimotor<br>Sensory                     | Dizziness<br>Muscle cramps<br>Myalgias<br>Neuromuscular complications<br>Ocular toxicity<br>Radicular neuropathy<br>Weakness                                                                                                                           |

(Continued on next page)

**TABLE 24-2.** Peripheral Neuropathy<sup>a,b</sup> (Continued)

| Classification                       | Agents                                                                                                                                                            | Type of Neuropathy            | Symptoms                                                                                                                                                         |
|--------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Small molecules                      | Bortezomib<br>Carfilzomib<br>Crizotinib<br>Imatinib<br>Ixazomib<br>Lorlatinib<br>Regorafenib<br>Selinexor<br>Selumetinib<br>Sorafenib<br>Sunitinib<br>Vemurafenib | Painful sensory               | Muscle wasting<br>Muscle weakness<br>Neuromuscular complications<br>Paresthesias<br>Reduced/lost DTR<br>Severe neuropathic pain<br>Tingling/burning sensation    |
| <b>Miscellaneous Antineoplastics</b> |                                                                                                                                                                   |                               |                                                                                                                                                                  |
| Chemotherapy                         | Arsenic trioxide<br>Eribulin<br>Ixabepilone<br>Sagopilone                                                                                                         | Sensorimotor<br>Sensory       | Dysesthesias<br>Impaired/lost sensation<br>Muscular weakness<br>Neuralgia<br>Neuropathic pain<br>Parasthesias<br>Reduced/lost DTR                                |
| Immune checkpoint inhibitors         | Atezolizumab<br>Cemiplimab-rwlc<br>Durvalumab<br>Ipilimumab<br>Nivolumab<br>Pembrolizumab                                                                         | Autonomic<br>Sensory<br>Motor | Facial nerve palsies<br>Gastrointestinal dysmotility<br>Neuropathic pain<br>Orthostasis<br>Paresthesias<br>Trigeminal neuralgia<br>Urinary retention<br>Weakness |
| Immunomodulatory agents              | Lenalidomide<br>Pomalidomide<br>Thalidomide                                                                                                                       | Autonomic<br>Sensory          | Bradycardia<br>Constipation<br>Impotence<br>Muscle cramps<br>Neuropathic pain<br>Paresthesias<br>Tremors                                                         |

<sup>a</sup>To date, peripheral neuropathy has not been reported with chimeric antigen receptor T cells.

<sup>b</sup>This table may not be inclusive of all agents associated with neurotoxicity.

<sup>c</sup>Coasting refers to worsening of neuropathy signs or symptoms after drug discontinuation.

*Note.* Based on information from AstraZeneca Pharmaceuticals, 2021; Bristol-Myers Squibb, 2021a, 2021b, 2021c; Dietrich, 2020; EMD Serono, 2021; Genentech, 2021; Haugh et al., 2020; Ibrahim & Ehrlich, 2020; Karyopharm Therapeutics, 2020; Merck, 2021; Pellacani & Eleftheriou, 2020; Pfizer, 2021a, 2021b; Regeneron Pharmaceuticals, 2021; Stone & DeAngelis, 2016; Taillibert et al., 2016; Takeda Oncology, 2021; Truven Health Analytics, 2017; Wick et al., 2016; Zajackowska et al., 2019.

- (2) Some evidence suggests that the activation of the trigeminovascular system could play a significant role in SMART syndrome (Dominguez & Malani, 2021; Singh et al., 2017)
- c) Incidence: SMART syndrome is rare, but the condition is likely underreported.
- d) Clinical manifestations: Symptoms can include headache, focal neurologic deficits, drowsiness, altered mental status, and seizures (Dominguez & Malani, 2021; Lim et al., 2016; Singh et al., 2017; Stone & DeAngelis, 2016).

#### e) Assessment

- (1) Radiographic imaging, such as magnetic resonance imaging (MRI) with gadolinium, may help rule out other differential diagnoses (e.g., second mass, radiation necrosis), but findings are otherwise non-specific and nondiagnostic (Dominguez & Malani, 2021).
- (2) Diagnosis is achieved by the patient report of symptoms, treatment history, careful neurologic examination, and the elimination of organic causes (Dominguez &

Malani, 2021; Lim et al., 2016; Singh et al., 2017; Stone & DeAngelis, 2016).

f) Collaborative management

- (1) Antimigraine therapies (e.g., valproic acid) have been used with some success to prevent the onset of SMART syndrome (Stone & DeAngelis, 2016).
- (2) Recent literature also supports using antiseizure medications, calcium channel blockers, and steroids to control vaso-reaction responses (de Oliveira Franco et al., 2021; Dominguez & Malani, 2021; Jia et al., 2018; Patel et al., 2020).

4. Leukoencephalopathy

a) Overview

- (1) Leukoencephalopathy includes the toxicity of treatment caused by injury to white matter, specifically when the myelin sheaths that cover nerve fibers degenerate (Kanda et al., 2018).
- (2) It is a late effect characterized by white matter changes on MRI with or without variable neurocognitive changes.

b) Pathophysiology: The exact pathophysiology of leukoencephalopathy is unknown but globally attributed to injury of the brain parenchyma and small blood vessel damage (Kanda et al., 2018).

c) Incidence

- (1) The incidence of leukoencephalopathy varies widely (5.4%–92%) according to radiation dose and type, when imaging was obtained, and how the diagnosis was achieved (Cummings et al., 2016).
- (2) Subclinical cases (e.g., mild or no symptoms) may not be recognized or are unreported.

d) Clinical manifestations

- (1) Patients may report no symptoms or a range of minor symptoms (mild cognitive impairment) to a progressive cognitive decline, including dementia, altered consciousness, ataxia, focal deficits, balance issues, and seizure (Bargiotas et al., 2019; Taillibert et al., 2016).
- (2) Gait abnormalities and urinary incontinence are noteworthy to correlate with higher severity (Bompaire et al., 2018).
- (3) Recent evidence also suggests a direct correlation between visual and postural or balance deficits (Bargiotas et al., 2019).
- (4) Although acute white matter injury in the immediate aftermath of treatment can lead to headache, fever, vomiting, drowsiness, and encephalopathy, symptoms are

more commonly experienced one month to a year following radiation.

e) Assessment

- (1) Diagnosis is achieved radiographically with MRI, which typically shows deep and periventricular white matter abnormalities characterized by T2WI or FLAIR hyperintensities in the absence of focal lesions (Cummings et al., 2016; Kanda et al., 2018).
- (2) Additional findings may include cortical atrophy and dilated ventricles, as well as necrosis and demyelination, if tissue is obtained for biopsy (Kanda et al., 2018).

f) Collaborative management

- (1) No specific treatment exists for leukoencephalopathy.
- (2) The focus is on palliative support for clinical manifestations.

5. Radiation necrosis

a) Overview: For cancers requiring radiation therapy to the head, radiation necrosis is a form of delayed cell injury and death of healthy brain tissue that results in the formation of single or multiple nodules (Winter et al., 2019).

b) Pathophysiology

- (1) Radiation exposure provokes damage to the vascular endothelium in the noncancerous neural tissue surrounding the original tumor or surgical bed.
- (2) The initiation of inflammation response leads to cell apoptosis and small artery thrombosis, arterial occlusion, and eventually tissue death (Ali et al., 2019).

c) Incidence

- (1) Incidence varies widely (5%–26%) according to how radiation necrosis is defined and ultimately diagnosed, the type of radiation, and the presence of concurrent systemic agents (Vellayappan et al., 2018).
- (2) Importantly, emerging evidence suggests that the incidence of radiation necrosis has increased as concomitant immunotherapy (e.g., ipilimumab), select targeted agents (e.g., BRAF inhibitors), and steroid therapy have become more accepted treatment modalities (Colaco et al., 2016; Kim et al., 2017; Patel et al., 2016; Winter et al., 2019).

d) Clinical manifestations

- (1) Patients typically present months to years after radiation treatment with new onset of neurologic symptoms resulting from a mass effect of the necrotic tissue plug.
- (2) Symptoms include headache, focal neurologic deficits, seizures, and cognitive impairment (Vellayappan et al., 2018).

## e) Assessment

- (1) Diagnostics can include MRI, MR perfusion, MR spectroscopy, positron-emission tomography-computed tomography, and diffusion-weighted images (Kanda et al., 2018; Vellayappan et al., 2018).
- (2) These scans often show an enhancing mass radiographically indistinguishable from tumor recurrence or progression.
- (3) Biopsy or surgical resection is often required to determine whether the mass represents true tumor progression/recurrence or radiation necrosis (Ali et al., 2019; Vellayappan et al., 2018; Winter et al., 2020).

## f) Collaborative management

- (1) No approved treatment exists, although numerous off-label treatment modalities for radiation necrosis have been reported in the literature, including anticoagulation with heparin or warfarin, hyperbaric oxygen, focused interstitial laser therapy, and bevacizumab (Co et al., 2020; Vellayappan et al., 2018; Winter et al., 2020).
- (2) Of these, bevacizumab is the most supported in the literature. Therapies for the second effects of brain swelling include systemic steroids (Tanguturi & Alexander, 2018; Vellayappan et al., 2018).
- (3) Left untreated, radiation necrosis typically self-resolves.

## 6. Pseudoprogression

## a) Overview

- (1) Pseudoprogression occurs when a CNS-based tumor increases in size radiographically during or immediately (first few weeks to six months) following active treatment with radiation therapy alone or with a combination of radiation and immunotherapy (Yekula et al., 2020).
- (2) Although the appearance of pseudoprogression on MRI can be similar to radiation necrosis, time is the primary distinction; pseudoprogression occurs in the immediate aftermath of treatment, whereas radiation necrosis presents months to years following treatment.

## b) Pathophysiology: The mechanism by which pseudoprogression occurs is poorly understood but is thought to be a secondary effect of blood-brain barrier breakdown, which causes edema and increases the uptake of contrast material (Yekula et al., 2020).

## c) Incidence

- (1) The incidence of pseudoprogression varies widely based on how it is defined and

which diagnostics are used (e.g., Response Assessment in Neuro-Oncology and Response Evaluation Criteria in Solid Tumors), with reports specifying the overall incidence across all categories of solid tumors ranging from less than 10% to as high as 30% in patients with high-grade gliomas (Park et al., 2020; Thust et al., 2018).

- (2) More recently, pseudoprogression has also been reported with the use of targeted therapies and immunotherapies (e.g., immune checkpoint inhibitors) (Thust et al., 2018).

## d) Clinical manifestations: Typically, pseudoprogression is a treatment-related effect. It can only be seen radiographically, and patients often do not report symptoms.

## e) Assessment

- (1) The enhancing lesion is seen on MRI and often followed serially until resolution.
- (2) Emerging evidence shows that perfusion MRI with radiomics and advanced techniques, such as perfusion-weighted imaging, MR spectroscopy, and amino acid positron-emission tomography, can help distinguish pseudoprogression in patients (Elshafeey et al., 2019; Galdiks et al., 2017; Rahman et al., 2020; Thust et al., 2018).

## f) Collaborative management

- (1) No approved treatment exists for pseudoprogression, and in the absence of symptoms, patients typically only require surveillance with serial imaging until the condition self-resolves.
- (2) However, for patients reporting persistent symptoms, a biopsy is recommended, and supportive therapies mirror those for radiation necrosis (Tanguturi & Alexander, 2018).

## C. Radiation-induced peripheral nervous system toxicity: radiation fibrosis syndrome

1. Overview: Radiation fibrosis syndrome describes specific and late toxicity of radiation therapy that causes progressive fibrotic sclerosis to the musculoskeletal, soft, neural, and cardiopulmonary tissues within the irradiation field (Stubblefield, 2017b). Specific forms of radiation fibrosis are lumbosacral plexopathy and brachial plexopathy.

## a) Lumbosacral plexopathy is a rare but serious form of radiation fibrosis affecting the lumbar or sacral plexuses following radiation therapy for pelvic-area cancers (e.g., cervical).

- b) Brachial plexopathy occurs in patients who have had radiation therapy directed at the chest, axillary region, thorax, or neck (e.g., radiation therapy for breast cancer), injuring the network of nerves (brachial plexus) that innervate the sensorimotor function of the shoulder, arm, and hand.
  2. Pathophysiology
    - a) The pathologic mechanism is not fully delineated but involves capillary network/vascular disruption, vascular endothelial damage, and microvascular injury with subsequent tissue sclerosis, fibrosis, atrophy, and disruption of the extracellular matrix (Purkayastha et al., 2019).
    - b) Ultimately, radiation treatment can trigger the inflammatory process, leading to granulation tissue formation and the activation of the coagulation system (Clark, 2018).
  3. Incidence
    - a) Radiation fibrosis syndrome is a late (months to years following radiation therapy) and rare effect, with incidence varying according to the cancer, specific radiation therapy, and radiation dose (Clark, 2018; Purkayastha et al., 2019).
    - b) Its occurrence is probably underestimated because it is not commonly evaluated by radiation oncologists and symptoms often are overlooked or attributed to other causes.
  4. Clinical manifestations
    - a) Skin changes may be seen in the radiation field. Symptoms vary according to site.
    - b) In head and neck cancers, radiation fibrosis can cause the inability to fully open the mouth, swallowing difficulties, and associated speech pathologies (Stubblefield, 2017a).
    - c) Skin changes at the radiation site can include slower healing, changes in pigmentation, and photosensitivity (Clark, 2018).
    - d) In lung cancer, postradiation pulmonary fibrosis manifests as difficulty breathing, dry cough, fatigue, and inspirational pain, resulting in decreased oxygen levels (Purkayastha et al., 2019).
    - e) Symptoms of lumbosacral plexopathy typically include lower leg pain; reduced sensation; different degrees of weakness, paresis, or paralysis; and urinary or fecal incontinence in severe cases.
    - f) Numbness, weakness, pain, or abnormal sensations (e.g., tingling, burning) are often reported along the wrist, hand, arm, or shoulder in brachial plexopathy (Purkayastha et al., 2019; Stubblefield, 2017a).
  5. Assessment
    - a) Diagnosis is based on the report of symptoms in the context of time, location, and dose of radiation therapy.
    - b) Histopathologic evaluation of fibrotic masses, if present, can provide a definitive diagnosis.
  6. Collaborative management
    - a) Fibrosis is a permanent effect of radiation therapy. No cure exists; therefore, pretreatment prevention of radiation toxicities through external beam radiation therapy techniques (e.g., intensity modulated, image guided) is recommended (Purkayastha et al., 2019).
    - b) Traditional treatment consists of education, physical therapy, occupational therapy, orthotics, and medication to increase function, decrease sensory abnormalities, and protect from further injury (Stubblefield, 2017a).
    - c) Other recommended therapies include nonsteroidal anti-inflammatory drugs and muscle relaxants for muscle pain and spasms and nerve-stabilizing drugs for neuropathic symptoms (Purkayastha et al., 2019).
    - d) Emerging evidence supports angiotensin-converting enzyme inhibitors for patients with lung radiation fibrosis syndrome and tyrosine kinase inhibitors and corticosteroids for those with skin fibrosis (Purkayastha et al., 2019).
- D. Chemotherapy-induced CNS toxicity
  1. Fatigue
    - a) Overview
      - (1) Fatigue, the feeling of extreme tiredness, is the most common CNS complication of cancer therapies and is not agent specific (Wick et al., 2016).
      - (2) Cancer-related fatigue (CRF) is an adverse effect of traditional chemotherapy agents, radiation therapy, targeted agents, and immunotherapies, including chimeric antigen receptor (CAR) T cells (Wick et al., 2016; Zhu et al., 2016; see Chapter 23).
    - b) Pathophysiology
      - (1) CRF occurs as either a direct effect of the cancer therapy itself (e.g., anemia, hormone changes) or an indirect effect through reactions with the immune system, specifically the release of cytokines (Cohen et al., 2019).
      - (2) Literature further suggests interdependent relationships and shared mechanisms with the greater disease process, as well as a patient's innate stress and coping responses (e.g., depression, anxiety) (Lacourt & Heijnen, 2017; Poort et al., 2020).
    - c) Incidence
      - (1) The incidence of CRF varies widely according to cancer diagnosis, disease

phase, and treatment modality, with patients with advanced cancer and those receiving anticancer therapies having the highest prevalence rates at greater than 60% (Al Maqbali et al., 2021).

- (2) Symptoms of CRF persist throughout cancer therapy and can last for up to two years post-treatment (Cohen et al., 2019).

d) Clinical manifestations

- (1) Patients with CRF commonly describe themselves as weak, tired, exhausted, slow, having no energy, feeling worn out, or unable to perform activities.
- (2) Severity of symptoms can vary throughout the course of treatment.

e) Assessment: CRF is a self-perceived symptom identified by patients. It may be assessed clinically using a validated patient-reported outcome measure, such as unidimensional or multidimensional tools (Mohandas et al., 2017).

f) Collaborative management

- (1) Acute fatigue management focuses on identifying associated target factors, such as anemia, depression, alterations in mood, or sleep disturbances.
- (2) Cognitive deficits, such as attention and memory issues, are strongly associated with fatigue severity, especially in breast cancer survivors (Cohen et al., 2019).
- (3) Effective strategies for reducing CRF include exercise, good nutrition, friend and family support, adequate rest, and purposeful relaxation (Mohandas et al., 2017; O'Regan et al., 2019).

## 2. Acute or chronic encephalopathy

a) Overview

- (1) *Encephalopathy* is a general term referring to a syndrome of overall brain dysfunction that commonly manifests as confusion and altered mental status. Encephalopathy may be acute or chronic.
- (2) The permeating symptom of all forms of encephalopathy is varying levels of altered mental status.
- (3) The exact pathologic mechanisms vary according to the agent and subtype of encephalopathy. Progressive multifocal leukoencephalopathy, for example, results from opportunistic infection in the setting of an immunocompromised host.
- (4) Toxic leukoencephalopathy is an encephalopathy specifically of white matter resulting from exposure to antineoplastic therapies or other toxic agents. In addition to treatment temporality (acute vs. chronic), specific types of toxic leukoencephalopathy are further distinguished by stability (e.g., reversible vs. permanent).

tion to treatment temporality (acute vs. chronic), specific types of toxic leukoencephalopathy are further distinguished by stability (e.g., reversible vs. permanent).

b) Acute encephalopathy

- (1) Acute encephalopathy emerges within a few hours or days after chemotherapy administration, often resolves spontaneously with complete recovery after discontinuation of the agent, and rarely confers long-term sequelae such as epilepsy (Fischer & Schmutzhard, 2017).
- (2) Acute encephalopathy is commonly associated with alkylating agents, antimetabolites, antihormonal agents, topoisomerase inhibitors, DNA-intercalating agents, antiangiogenic agents, and immunomodulatory agents (Dietrich, 2020). Specific agents such as methotrexate, ifosfamide, and cytarabine are highly associated with acute encephalopathy.
- (3) Acute encephalopathy can develop as a constellation of symptoms, including focal neurologic deficits, neurobehavioral problems, seizures, or alterations in consciousness.
- (4) Acute encephalopathy typically self-resolves with discontinuation of the agent.

c) Posterior reversible encephalopathy syndrome (PRES)

(1) Pathophysiology

(a) PRES is an acute leukoencephalopathy that occurs with multiple anticancer agents, particularly certain tyrosine kinase inhibitors (e.g., imatinib), as well as immunosuppressants (e.g., cyclosporine, tacrolimus) used for patients undergoing allogeneic stem cell transplant (Ridgeway et al., 2020). It also can occur in patients who have received CAR T cells.

(b) Other classes of chemotherapy agents have been associated with PRES, including platinum analogs (e.g., cisplatin, carboplatin), folate antagonists (e.g., methotrexate), antimetabolites (e.g., gemcitabine, 5-fluorouracil), vinca alkaloids (e.g., vincristine), and targeted agents (e.g., bevacizumab, ramucirumab, rituximab) (Cacho-Díaz et al., 2019; Dietrich, 2020; Janjua et al., 2017; Kaur et al., 2020; Singer et al., 2015).



- (2) Clinical manifestations
  - (a) Somnolence and lethargy are the first reported symptoms by patients (Janjua et al., 2017).
  - (b) The most common symptoms cited in the literature include headache, seizure, altered mental status (e.g., confusion), and visual changes ranging from blurred vision to cortical blindness (Janjua et al., 2017).
  - (c) Other symptoms associated with PRES include nausea, vomiting, and focal neurologic deficits.
  - (d) Hypertension is the most common condition associated with PRES, presenting in 6%–72% of cases (Janjua et al., 2017).
  - (e) It is thought that hypertension, impaired autoregulation, and hyperperfusion collectively play a part in the onset of PRES (Janjua et al., 2017).
  - (f) Status epilepticus, one of the most severe and life-threatening complications, can develop in 3%–13% of cases (Fischer & Schmutzhard, 2017).
- (3) Assessment: Radiographically, PRES is characterized by vasogenic edema throughout the brain.
- (4) Collaborative management
  - (a) Treatment is primarily supportive to reduce the severity of symptoms (e.g., analgesic for headache) and manage blood pressure.
  - (b) Magnesium levels should be monitored to prevent hypomagnesemia in patients with PRES (Fischer & Schmutzhard, 2017).
  - (c) Intensive care monitoring and treatment are indicated in 40% of cases for more severe complications, such as status epilepticus, intracranial hypertension, intracerebral hemorrhage, and cerebral ischemia (Fischer & Schmutzhard, 2017).
  - (d) Discontinuation of the drug is necessary to reduce the risk of progression to irreversible cytotoxic edema.
  - (e) Symptoms of PRES improve or dissipate entirely with drug discontinuation and supportive therapy in 84% of patients (Fischer & Schmutzhard, 2017).
  - (f) The mortality rate is 8%–19% (Kaur et al., 2020).
  - (g) Early recognition of symptoms is essential to prevent the development of serious complications.
- d) Encephalitis: Encephalitis, or autoimmune encephalitis, is an immune-related event in which severe brain inflammation occurs that can cause serious adverse effects.
  - (1) Pathophysiology
    - (a) Immune checkpoints, such as programmed cell death protein 1, programmed cell death-ligand 1, and cytotoxic T-lymphocyte antigen 4, are integral for preventing autoimmunity and are widely distributed throughout healthy tissues, including the CNS (Haugh et al., 2020).
    - (b) Immune checkpoint inhibitors block these pathways and can produce autoimmune toxicities in the CNS.
    - (c) A proliferation of lymphocytes, including T lymphocytes, has been demonstrated in the cerebrospinal fluid of individuals with autoimmune encephalitis from immune checkpoint inhibitors (Kopecký et al., 2018; Sanchis-Borja et al., 2020).
  - (2) Incidence: The incidence of immune checkpoint inhibitor-induced encephalitis is less than 1% (Xu et al., 2019); however, it is increasingly being reported in the literature as immune checkpoint inhibitors become part of the standard of care for many cancer types.
  - (3) Clinical manifestations
    - (a) Immune checkpoint inhibitor-induced encephalitis is associated with significant morbidity and a 13% mortality rate. It has been seen in the settings of melanoma, non-small cell lung cancer, and urinary malignancies (Marini et al., 2021).
    - (b) Immune checkpoint inhibitor-induced encephalitis can be difficult to recognize and should be considered when symptoms of CNS toxicity are present, such as mental status changes, mild fatigue, headache, fever, weakness, seizure, or neurologic deficits (Haugh et al., 2020).
    - (c) Immune checkpoint inhibitors, such as ipilimumab, nivolumab, pembrolizumab, cemiplimab, atezolizumab, avelumab, and durvalumab, have been associated with severe encephalitis (Marini et al., 2021).



- (d) In the case of melanoma, where immune checkpoint inhibitors are commonly used, autoimmune toxicity can cause CNS demyelination (Zukas & Schiff, 2018).
  - (e) Patients who have an autoimmune disorder, such as multiple sclerosis, can be at higher risk of relapse or worsening symptoms when receiving immune checkpoint inhibitors as part of cancer treatment and should be closely monitored (Haugh et al., 2020; Zukas & Schiff, 2018).
- (4) Assessment
- (a) Diagnosis is achieved with neurologic examination and the presence of abnormalities on MRI and in cerebrospinal fluid.
  - (b) On brain MRI, the most common abnormality is hyperintensity involving the medial temporal lobes (Haugh et al., 2020; Marini et al., 2021).
  - (c) Analysis of cerebrospinal fluid obtained from lumbar puncture demonstrates inflammatory alterations in 93% of patients and elevated protein and leukocytes (Marini et al., 2021).
  - (d) In metastatic cancer, immune checkpoint inhibitor-induced encephalitis is more challenging to diagnose due to other CNS effects of disease progression (Haugh et al., 2020).
- (5) Collaborative management
- (a) Early identification of the causative agent and appropriate management of symptoms are key to preventing adverse outcomes (Haugh et al., 2020).
  - (b) Current treatment consists of discontinuation of the drug, inpatient monitoring, and high-dose IV steroids (Marini et al., 2021).
  - (c) IV immunoglobulin or rituximab have also been used for severe or progressive symptoms of autoimmune encephalitis (Haugh et al., 2020).
  - (d) Literature suggests more data are needed to determine best practice recommendations for managing immune checkpoint inhibitor-induced encephalitis.
- e) Chronic encephalopathy
- (1) Chronic encephalopathy is typically observed more than six months post-treatment and even several years beyond treatment (Taillibert et al., 2016).
  - (2) It is generally irreversible and occasionally progressive. No cure or effective treatment exists for chronic encephalopathy.
  - (3) Clinical manifestations
    - (a) Patients usually report mild to moderate neurocognitive deficits, such as memory impairment or inability to focus. More severe symptoms, such as ataxia, urinary incontinence, and spasticity, correlate with more significant neurotoxicity.
    - (b) Chronic encephalopathy is frequently described as “chemobrain” or “chemo fog,” in which patients experience problems with memory function and multitasking. Chemobrain may reduce the ability to perform socially and professionally, decreasing quality of life (Dietrich, 2020).
    - (c) Some patients report no symptoms.
- f) Progressive multifocal leukoencephalopathy (PML)
- (1) Pathophysiology
    - (a) PML is a neuroinfectious disease-causing demyelinating injury to the CNS that can manifest during treatment or months to years following treatment with immunomodulatory therapy.
    - (b) PML is caused by reactivation of latent John Cunningham virus, a human polyomavirus that is normally innocuous and present in 50%–70% of healthy adults (Bohra et al., 2017).
    - (c) Treatment-related immunosuppression with brentuximab, rituximab, alemtuzumab, obinutuzumab, and ofatumumab therapy leads to lytic infection of CNS white matter with resultant demyelination (Bohra et al., 2017).
  - (2) Incidence
    - (a) The incidence of PML in the setting of hematologic malignancies is rare (0.07%).
    - (b) PML may be underreported given the challenges of achieving diagnosis (Bohra et al., 2017).
    - (c) However, with the increasing use of immunomodulatory therapies in

oncology, clinicians should be familiar with PML as a differential diagnosis.

(3) Clinical manifestation

(a) Patients should be monitored closely for CNS symptoms that could indicate encephalopathy.

(b) Symptoms can include hemiparesis, visual impairment, altered mental status, ataxia, dysmetria, dysarthria, headache, vertigo, seizures, sensory deficits, parkinsonism, aphasia, and neglect syndromes (Bohra et al., 2017).

(4) Assessment

(a) Diagnosis can be difficult, as the list of differential diagnoses is extensive (e.g., brain metastases, aseptic meningitis) but is typically achieved based on the report of symptoms, neurologic examination, and treatment context and timing.

(b) Because of the structural changes within white matter, PML can often be identified radiographically via MRI. A brain biopsy is required for a definitive diagnosis of PML.

(5) Collaborative management

(a) PML is untreatable, progressive, and nearly always fatal (90% fatality rate) (Bohra et al., 2017).

(b) The use of medications such as mefloquine (a drug used to treat malaria) and mirtazapine (inhibitor of serotonin 5-HT<sub>2A</sub> receptor) to treat PML remains investigational (Bohra et al., 2017).

### 3. Focal deficits

#### a) Overview

(1) Focal neurologic deficits are limited failures of neurologic function that affect a specific part of the body.

(2) Vision, speech, and hearing impairments during or immediately following cancer treatment are considered focal neurologic toxicities. Isolated sensory and motor losses are other examples.

#### b) Pathophysiology

(1) All focal nerve deficits originate from injury to the nerve, either as a direct result of chemotherapy or as a secondary effect (e.g., swelling).

(2) The exact pathogenesis of cranial nerve involvement is uncertain. Focal defi-

cits may also be a direct consequence of malignancy.

c) Incidence: Transient focal deficits are relatively common over the cancer trajectory and are sometimes difficult to attribute exclusively to cancer or its treatment.

#### d) Clinical manifestations

(1) Each cranial nerve operates a distinct neurologic function and can help localize neurotoxic injury (see Table 24-3).

(2) For example, double vision and oromandibular dystonia have been reported with capecitabine use and correlated with neurotoxic palsy of cranial nerve VI (Cengiz et al., 2018; Dasgupta et al., 2010).

(3) Literature suggests vision loss and visual-motor integration skill impairment with certain drugs (e.g., carmustine, fludarabine) (Pinner & Tierney, 2020).

(4) Ipilimumab, an immune checkpoint inhibitor, is known to cause optic neuritis and focal deficits in some patients (Zukas & Schiff, 2018).

(5) Carboplatin is known to cause ototoxicity in patients with neuroblastoma (Pinner & Tierney, 2020).

(6) Platinum-based agents can cause irreversible hearing impairment and tinnitus in 20%–40% of patients (Dietrich, 2020).

e) Assessment: Diagnosis is achieved with a careful neurologic examination.

f) Collaborative management: Treatment typically involves supportive therapy or, in severe cases, discontinuation of the agent.

### 4. Cerebellar syndrome

a) Overview: Neurotoxic injury to the cerebellum may result in cerebellar syndrome, characterized by ataxia, dysmetria, dizziness, nystagmus, and gait imbalance.

#### b) Pathophysiology

(1) Cerebellar syndrome has been reported as an acute to subacute event with traditional chemotherapy agents, including capecitabine, cytarabine (high dose), 5-fluorouracil, oxaliplatin, procarbazine, and vincristine.

(2) It is generally dose related and self-limiting, but 20%–30% of patients may experience permanent dysfunction secondary to loss of Purkinje cells in the cerebellum (Dietrich, 2020).

(3) Exact pathologic mechanisms vary according to the agent, but symptoms arise from loss or delay of nerve conduction through the cerebellum, which is

responsible for coordinating muscle activity and movement.

c) Incidence

- (1) Overall, the incidence of cerebellar syndrome is low, with variation by the agent.
- (2) Literature shows that high-dose cytarabine is the agent most associated with cerebellar syndrome, occurring in 10%–20% of patients receiving high-dose therapy (Dietrich, 2020).

d) Risk factors

- (1) CNS effects directly correlate with the degree to which a drug passes the blood–

brain barrier (Cintrón-García & Guddati, 2020).

- (2) Prior brain irradiation combined with other therapies can also lead to a greater risk of CNS toxicity (Cintrón-García & Guddati, 2020).
- (3) Several risk factors have been associated with the development of CNS toxicity, including concurrent or prior brain irradiation, older age, renal dysfunction, hepatic dysfunction, presence of comorbidities (e.g., hypertension, cardiovascular disease), and previous history of neurologic dysfunction (Dietrich, 2020).

**TABLE 24-3.** Focal Deficits Involving the Cranial Nerves

| Signs and Symptoms                                                                                               | Cranial Nerve | Name             | Origination    | Function                                                                                                                                                                           |
|------------------------------------------------------------------------------------------------------------------|---------------|------------------|----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Loss of smell (anosmia)                                                                                          | I             | Olfactory        | Olfactory bulb | Special sensory: smell                                                                                                                                                             |
| Visual disturbances; vision loss                                                                                 | II            | Optic            | Thalamus       | Special sensory: vision                                                                                                                                                            |
| Loss of pupillary light reflex; papilledema; ptosis; double vision (diplopia); blurry vision                     | III           | Oculomotor       | Midbrain       | Motor: eyeball movement; controls eyelid<br>Parasympathetic: pupil constrictor                                                                                                     |
| Diplopia; nystagmus                                                                                              | IV            | Trochlear        | Midbrain       | Motor: eyeball movement                                                                                                                                                            |
| Loss of sensations (see function column); difficulty chewing, abnormal jaw-jerk reflex                           | V             | Trigeminal       | Pons           | Motor: chewing muscles<br>Sensory: touch, pain, temperature, vibration for face, mouth, anterior two-thirds of tongue                                                              |
| Strabismus; nystagmus; diplopia                                                                                  | VI            | Abducens         | Pons           | Motor: eyeball movement                                                                                                                                                            |
| Facial paresis or plegia; loss of taste                                                                          | VII           | Facial           | Pons           | Motor: face muscles<br>Sensory: sense near ears<br>Special sensory: taste in anterior two-thirds of tongue                                                                         |
| Hearing loss; balance issues                                                                                     | VIII          | Auditory         | Pons/medulla   | Special sensory: hearing and balance                                                                                                                                               |
| Absent gag; impaired or absent swallow; loss of taste; loss of pharyngeal movement                               | IX            | Glossopharyngeal | Pons/medulla   | Motor: pharyngeal movement<br>Sensory: middle ear; pharynx, posterior one-third of tongue<br>Parasympathetic: parotid gland                                                        |
| Absent gag; impaired or absent swallow; loss of velar movement; loss of voice or hoarseness, dyspnea, dysarthria | X             | Vagus            | Medulla        | Motor: pharyngeal and laryngeal muscles<br>Sensory: pharynx and blood pressure<br>Special sensory: taste from epiglottis/pharynx<br>Parasympathetic: heart, lungs, digestive tract |
| Droopy shoulder, movement of neck                                                                                | XI            | Spinal accessory | Medulla        | Motor: neck and shoulder muscles                                                                                                                                                   |
| Loss of tongue movement; tongue fasciculation, tongue atrophy                                                    | XII           | Hypoglossal      | Medulla        | Motor: tongue muscles                                                                                                                                                              |

Note. From *Neuroanatomy for Speech Language Pathology and Audiology* (pp. 84–85), by M.H. Rouse, 2016, Jones and Bartlett Learning. Copyright 2016 by Jones and Bartlett Learning, www.jblearning.com. Adapted with permission.

## e) Clinical manifestations

- (1) Early signs include nystagmus, speech difficulties (e.g., dysarthria), uncoordinated movements, abnormal gait, and trouble writing (e.g., dysmetria). Somnolence, encephalopathy, and nausea can also occur (Dietrich, 2020).
- (2) Symptoms typically resolve with drug discontinuation, but up to 30% of patients suffer permanent cerebellar injury (Dietrich, 2020).
- (3) Cerebellar atrophy is a late effect that can develop several months after using cytarabine (Dietrich, 2020).

## f) Assessment

- (1) Diagnosis is achieved by reporting symptoms with careful neurologic examination before each infusion of agents known to cause cerebellar syndrome.
- (2) This includes assessment of patient coordination (e.g., finger-to-nose and finger-to-finger test, rapid alternating hand movements, ability to write), speech pattern, gait and balance, and presence of abnormal eye movements (e.g., nystagmus).
- (3) When signs and symptoms are present, the causative medication should be held, and the prescriber should be notified immediately.

## g) Collaborative management

- (1) Symptoms typically resolve over time or with discontinuation of therapy.
- (2) Depending on the extent of injury, some sequelae may be permanent.
- (3) Early recognition of treatment-induced adverse neurologic effects is essential to avoid more severe or permanent neural injury to the brain (Dietrich, 2020).

## 5. Adverse cerebrovascular events

## a) Overview

- (1) Cerebrovascular events are a constellation of clinical syndromes that disrupt the blood supply to the brain with a resultant neurologic symptom or symptom complex.
- (2) Cerebrovascular events are classified according to etiology, location, and duration of symptoms.
- (3) Common cerebrovascular events manifesting in the setting of chemotherapy include thromboembolism, intracranial hemorrhage, and ischemic stroke.

(a) Cerebral thromboembolism is a blood clot that occludes the small and large cerebral arteries.

(b) Intracranial hemorrhage is bleeding inside the cranial vault, resulting in accumulation of blood and, frequently, increased intracranial pressure.

(c) Ischemic stroke is the sudden loss of blood circulation to an area of the brain, resulting in a corresponding loss of neurologic function. It occurs in the setting of thrombotic or embolic occlusion of a cerebral artery (American Stroke Association, n.d.).

## b) Pathophysiology

- (1) Cancer stimulates the coagulation system, predisposing patients to a baseline hypercoagulable or prothrombotic state.
- (2) Many cancer therapies further potentiate this risk of thrombosis through procoagulant release, endothelial damage, or stimulation of tissue factors. Ischemic stroke, a direct effect of arterial occlusion by thromboembolism, is associated with chemotherapies (e.g., pegaspargase, cisplatin), immunotherapies (e.g., thalidomide), antiangiogenesis monoclonal antibodies (e.g., bevacizumab, ramucirumab), targeted therapies (e.g., lenvatinib, osimertinib), and hormone therapies (e.g., tamoxifen) (Nasser et al., 2020).
- (3) In contrast, intracranial hemorrhage, including intratumoral hemorrhage, in patients with cancer is typically a secondary effect of disseminated intravascular coagulation, thrombocytopenia due to bone marrow suppression, or vitamin K deficiency.
- (4) An increased risk of thromboembolic events exists in the setting of bevacizumab, and a 24% incidence of stroke or transient ischemic attack has been reported in patients undergoing hematopoietic stem cell transplantation (Ridge-way et al., 2020).

## c) Incidence

- (1) Incidence varies according to the type of cancer, event, and agent.
- (2) Hematologic cancers show the highest association with cerebrovascular events, followed by brain tumors (Cordelli et al., 2017).
- (3) The highest incidence of intracranial hemorrhage is noted with acute myeloid leukemia (Cordelli et al., 2017).
- (4) Risk of hemorrhage or ischemic stroke is higher with bevacizumab when given

alone or in combination with chemotherapy (Nasser et al., 2020).

- (5) In some instances, the risk of stroke is higher when chemotherapy drugs are given in combination with other drugs, although the exact pathophysiology is unknown (Stone & DeAngelis, 2016).
- (6) For example, the risk of stroke is higher when cisplatin is used in combination with other chemotherapy drugs (Stone & DeAngelis, 2016).
- (7) L-Asparaginase increases the risk of venous sinus thrombosis, leading to potentially serious cardiovascular events, such as stroke, intracranial hemorrhage, and seizures (Cintrón-García & Guddati, 2020; Stone & DeAngelis, 2016).

*d) Clinical manifestations*

- (1) The cardinal clinical feature of many cerebrovascular events is painful headaches.
- (2) Additional symptoms include nausea, vomiting, altered mental status, seizure, or focal neurologic symptoms.
- (3) Depending on when a patient is seen and the underlying cause, the deficit may be stable, progressive, or completely resolved.
- (4) Methotrexate-induced neurotoxicity can specifically present as stroke-like manifestations, including symptoms such as hemiparesis, dysphasia, and seizures (Dietrich, 2020).

*e) Assessment:* Diagnosis is made radiographically via computed tomography or MRI (American Stroke Association, n.d.).

*f) Collaborative management*

- (1) Patients with thromboembolism and ischemic stroke typically are given multimodal therapy, such as anticoagulation, thrombolysis, and platelet inhibition.
- (2) Hemorrhage may require neurosurgical intervention to decompress the brain, initiate invasive pressure monitoring, or evacuate a clot. Supportive treatment includes pain medication, steroids, and antiseizure medication.

## 6. Aseptic meningitis

*a) Overview*

- (1) Aseptic meningitis is irritation and inflammation of the meninges in the absence of infection.
- (2) It is the most commonly reported toxicity of intrathecal chemotherapy, especially methotrexate and cytarabine.
- (3) Other agents that induce aseptic meningitis include cetuximab, ipilimumab, IV

immunoglobulin, high-dose cytarabine, and rituximab.

*b) Pathophysiology*

- (1) The pathologic mechanism of aseptic meningitis is indeterminate and likely varies by the agent.
- (2) For example, aseptic meningitis following cetuximab administration is thought to stem from an allergic hypersensitivity reaction or serum immunoglobulin crossing the blood–brain barrier, causing meningeal inflammation (Maritaz et al., 2016).

*c) Incidence*

- (1) Incidence of aseptic meningitis varies widely according to agent and dose, but it is usually observed after intrathecal drug administration.
- (2) For example, meningitis following intrathecal methotrexate administration is reported in 10%–60% of patients (Dietrich, 2020).
- (3) However, the incidence of meningitis following cetuximab administration is much lower, with fewer than a dozen reports in the literature (Maritaz et al., 2016).

*d) Clinical manifestations:* Symptoms include low-grade fever, headache, stiff neck, back and neck pain, nausea, vomiting, lethargy, photophobia, and increased cell presence (e.g., white blood cells, protein) in the cerebrospinal fluid (Dietrich, 2020; Taillibert et al., 2016).

*e) Assessment*

- (1) The diagnosis is usually presumptive based on symptoms, temporality, and chemotherapy route.
- (2) Cerebrospinal fluid obtained from lumbar puncture generally shows mild pleocytosis and protein elevation (Dietrich, 2020).

*f) Collaborative management*

- (1) Prophylactic dosing with dexamethasone prior to intrathecal chemotherapy may help reduce the risk of aseptic meningitis.
- (2) Symptoms can be managed with supportive therapy, which includes analgesics, antiemetics, steroids if not already given prophylactically, and IV fluids.
- (3) Otherwise, spontaneous recovery is seen within days without any neurologic sequelae when the agent is discontinued.
- (4) Aseptic meningitis is considered a stand-alone event and does not indicate similar reactions with subsequent administration of the same drug (Dietrich, 2020).

## 7. Myelopathy

a) Overview: Myelopathy is a rare complication of swelling and spinal cord compression during or following intrathecal chemotherapy administration, such as methotrexate and cytarabine (Tariq et al., 2018).

## b) Pathophysiology

- (1) The etiology of myelopathy following intrathecal chemotherapy remains unclear.
- (2) Symptoms develop over hours or days following the intrathecal infusion of methotrexate (Tariq et al., 2018).
- (3) Ultimately, spinal cord dysfunction results from swelling and cord compression.

c) Incidence: Myelopathy as a complication of intrathecal chemotherapy is rare in adults (approximately 3%), with most cases occurring in the pediatric population (Cordelli et al., 2017).

d) Clinical manifestations: Symptoms include low back pain or leg pain followed by sensory loss or motor deficits in the lower extremities (e.g., paraplegia), flaccid paresis (e.g., loose and floppy limbs), and bowel or bladder incontinence or retention (Cordelli et al., 2017).

e) Assessment: MRI is the most sensitive radiologic technique in diagnosing myelopathy, but MRI abnormalities are nonspecific and include T2 hyperintensity and contrast enhancement. Elevation in cerebrospinal fluid protein levels is also evident on lumbar puncture (Cordelli et al., 2017).

## f) Collaborative management

- (1) No approved treatment exists for chemotherapy-induced myelopathy. Recent literature supports the use of high doses of S-adenosylmethionine, folinate, methionine, and cyanocobalamin (vitamin B<sub>12</sub>) to reverse toxicity and improve clinical symptoms (Tariq et al., 2018).
- (2) Symptoms and swelling are generally reversible, but in some instances, symptoms are rapidly progressive, and recovery is only partial (Cordelli et al., 2017).
- (3) Deficits can be permanent in some cases (Tariq et al., 2018).

## 8. Seizures

## a) Definition

- (1) A seizure is the manifestation of an abnormal, hypersynchronous electrical discharge of a population of cortical neurons.
- (2) This discharge may produce symptoms or objective signs (e.g., clinical seizure) or may be subclinical, materializing only on an electroencephalogram.

## b) Pathophysiology

- (1) The underlying etiology of seizures in patients with cancer can be complex, involving anatomic and metabolic disruptions caused by brain tumors, tumor- or medication-related stroke or opportunistic infection, chemotherapy, or neuro-radiation therapy. Seizures may be caused directly by agents themselves (e.g., busulfan [used commonly during stem cell transplantation]) or may result from hyponatremia as a secondary effect of hormone or electrolyte imbalances (Taillibert et al., 2016).
- (2) For example, syndrome of inappropriate antidiuretic hormone secretion is a known effect of vinca alkaloids and cisplatin that can result in hyponatremia, leading to severe confusion, coma, and seizures (Bénit & Vecht, 2016).
- (3) Cisplatin-induced renal injury can result in salt wasting, hyponatremia, and seizures (Bénit & Vecht, 2016).
- (4) Targeted therapies that inhibit epidermal growth factor receptor pathways, such as the monoclonal antibodies cetuximab and panitumumab and the tyrosine kinase inhibitors gefitinib and erlotinib, also cause secondary electrolyte depletion, which increases the risk of seizure (Wick et al., 2016).
- (5) Seizures also result from interferon and interleukin-2, which cause cytokine release in CAR T-cell therapy (Latchford & Tierney, 2020).

## c) Incidence

- (1) Incidence varies according to the cancer, location, and agent.
- (2) Busulfan, an agent used during conditioning for stem cell transplantation, carries a 10% risk of seizures in the absence of prophylactic anticonvulsants (Ridgeway et al., 2020).
- (3) The seizure risk decreases to 0%–5.5% with prophylaxis (Latchford & Tierney, 2020).
- (4) For patients with primary brain tumors, more than 65% with gliomas and 33% with meningiomas will have epilepsy (Bénit & Vecht, 2016).
- (5) For patients with systemic cancer, the incidence of seizures is higher. Approximately 60% of patients with brain metastases will develop epilepsy (Bénit & Vecht, 2016).

d) Clinical manifestations: Signs and symptoms of a seizure can include temporary confusion, staring



spells, involuntary jerking or violent movements of the arms and legs, and altered mental status, including loss of consciousness.

e) Assessment

- (1) A thorough neurologic examination is performed to explore differential diagnoses.
- (2) A diagnosis is typically achieved via electroencephalogram, although a witnessed tonic-clonic seizure can be enough to initiate treatment.

f) Collaborative management

- (1) Patients with brain tumors have reported seizures as a significant cause of distress, which is often associated with the perception of poor quality of life (Grant, 2017).
- (2) Proper management of these symptoms is key, and typical treatment includes antiepileptics.
- (3) In the case of high-dose busulfan, prophylaxis with antiepileptics prior to therapy is standard practice, as the risk of seizure is significantly high (Ridgeway et al., 2020).
- (4) Literature suggests that up to 66% of brain tumors have seizure foci that can be surgically resected, resulting in the elimination of seizures in 65%–85% of cases (Chen et al., 2018).

## 9. Headache

a) Overview: Headache is pain with or without pressure in the head.

b) Pathophysiology

- (1) Headache is one of the most common complications in cancer treatment.
  - (a) Headache can be caused directly by the mass effect of intracranial malignancy, malignant infiltration of the meninges or pituitary gland, or as a direct effect of anticancer therapies, such as radiation therapies, chemotherapies (e.g., 5-fluorouracil, procarbazine), targeted therapies (e.g., imatinib, rituximab, infliximab), and immunotherapies (e.g., CAR T cells, ipilimumab) (Ridgeway et al., 2020; Stone & DeAngelis, 2016).
  - (b) As a result, attributing a single causative agent is challenging, but the temporality of headache emergence to treatment can be instructive.
  - (c) Mechanisms of action are varied based on the agent. For example, a headache during rituximab infusion or after CAR T-cell infusion likely results from the release of inflamma-

tory cytokines (Ridgeway et al., 2020; Wick et al., 2016).

- (2) Headache can also be a secondary effect of treatment. Examples include postprocedural complications of cancer diagnostics, such as a lumbar puncture or brain biopsy; stress, fatigue, anxiety, or sleep disturbances resulting from cancer or its treatment; cancer- or treatment-associated anemia; and hypercalcemia and dehydration from vomiting and diarrhea.

c) Incidence: Incidence varies widely according to the causative agent.

d) Clinical manifestation: Patients may report pain, tightness, or pressure in the head or upper neck.

e) Assessment: Diagnosis is based on patient self-report.

f) Collaborative management: Treatment typically involves administering analgesics and, if warranted, intervention to correct the proximate cause, such as a blood patch for post-lumbar puncture headache or correction of anemia or hypercalcemia.

## E. Peripheral neuropathy (PN): general neurotoxicities

1. Overview: PN is damage to nerve cells, nerve fibers (axons), and nerve coverings (myelin) due to exposure to a neurotoxic chemotherapy agent that inhibits or decelerates nerve signals. The three major categories of PN are sensory, motor, and autonomic (Clark, 2018).

a) Sensory neuropathy

(1) Sensory neuropathy is known as glove-and-stocking neuropathy. It results from damage to sensory nerves causing problems with sensation in distal portions of the limb (e.g., the ability to feel pain or light touch) (Zajackowska et al., 2019).

(2) This type of neuropathy is often progressive and can decrease overall proprioception, leading to ambulatory difficulties (Clark, 2018).

b) Motor neuropathy is less common than sensory neuropathy and leads to injury to motor nerves, affecting movement (Clark, 2018).

c) Autonomic neuropathy is the impairment of the nonsensory, involuntary nervous system that controls and regulates smooth muscles, cardiac muscles, and glands (e.g., nerves innervating the heart, bladder, and salivary glands).

## 2. Pathophysiology

a) Antineoplastics differentially impair specific structures within the neuron according to their mechanism of action.



*b)* In general, the predominant pathophysiologic mechanism of PN across all chemotherapy agents is induction of mitochondrial abnormalities and inhibition of mitochondrial function (Brewer et al., 2016).

*c)* PN can be broadly attributed to the resultant demyelination and disruption in axonal transport and resulting degeneration (Clark, 2018).

### 3. Incidence

*a)* Incidence and severity of PN vary by the specific type (sensory, motor, or autonomic), agent, agent combinations, and dosages. PN is likely under-reported.

*b)* In aggregate, PN occurs in 30%–70% of patients receiving neurotoxic chemotherapy, most notably platinum agents, vinca alkaloids, taxanes, proteasome inhibitors, antimicrotubules, anti-angiogenesis agents, and immunotherapy agents (e.g., immune checkpoint inhibitors) (Clark, 2018; Marini et al., 2021; Staff et al., 2017; Zajączkowska et al., 2019).

### 4. Clinical manifestations

#### *a)* Sensory

(1) Sensory neuropathies may be subtle and not consistently present during physical examination.

(2) Symptoms may be positive, in which sensations are present in the absence of external stimuli and perceived as tingling, burning, pins and needles, or pain typically described as stabbing or shooting.

(3) Sensory disturbances can also manifest as negative phenomena (e.g., numbness, loss of sensation, impaired proprioception), in which sensations are completely absent with external stimulation; for example, patients report the inability to feel a pinprick.

#### *b)* Motor

(1) Motor neuropathies may manifest as weakness, muscle fatigue, or atrophy.

(2) Patients also may report abnormally frequent and painful muscle cramps or fasciculation, causing problems with ambulation due to gait and balance issues and manual dexterity (Zajączkowska et al., 2019).

(3) Motor neuropathy may co-occur with sensory neuropathy (i.e., sensorimotor neuropathy).

*c)* Autonomic: Autonomic neuropathy is seen most commonly with vinca alkaloids and can be associated with orthostatic hypotension, erectile dysfunction, and bowel and bladder dysfunction,

including paralytic ileus, constipation, and urinary retention.

### 5. Assessment

*a)* Results from the physical examination may be normal or show a sensory loss.

*b)* Loss of the Achilles tendon reflex is usually the first clinical sign of PN (Tzatha & DeAngelis, 2016).

*c)* Nerve conduction studies and an electromyogram can assist with diagnostic evaluation but can be costly (Ibrahim & Ehrlich, 2020).

*d)* Newer web-based self-assessment tools have been developed and have shown to be an effective approach to identifying and grading PN (Ibrahim & Ehrlich, 2020).

### 6. Collaborative management

*a)* PN is managed by empirical dose modifications or discontinuation of treatment at the discretion of the treating provider.

*b)* Treatment of urinary retention may include intermittent catheterization until recovery of function.

*c)* Pharmacologic agents occupy a key role in managing PN symptoms.

(1) Adjuvant therapies, often used with opioid analgesics, are the cornerstone of treatment.

(2) These therapies include anticonvulsants (e.g., gabapentin, pregabalin), antidepressants (e.g., tricyclics, serotonin-norepinephrine reuptake inhibitors), and ion channel blockers (e.g., lidocaine) (National Comprehensive Cancer Network [NCCN], 2022a; Oncology Nursing Society, 2019).

(3) Additional evidence suggests that the use of venlafaxine and duloxetine may benefit sensory and motor neuropathies (Farshchian et al., 2018; Ridgeway et al., 2020).

## F. Common antineoplastics conferring increased neurotoxicity

### 1. Chemotherapy

#### *a)* Vinca alkaloids

(1) Vinca alkaloids (e.g., vinblastine, vincristine, vinorelbine) inhibit cell proliferation and promote cytotoxicity by direct binding to beta-tubulin, a critical component of microtubules (Pellacani & Eleftheriou, 2020).

(2) Microtubules perform the essential function of aligning chromosomes during metaphase (the third phase of mitosis) (Ibrahim & Ehrlich, 2020).

- (3) The binding of agents to the microtubules ultimately results in inhibition of mitotic spindle function and arrests cancer cells in metaphase, rendering them unable to divide (Pellacani & Eleftheriou, 2020).
  - (4) However, throughout the nervous system, microtubules also help direct axonal transport of neuronal signals.
  - (5) PNs of vinca alkaloids that target microtubules result from interruption of the axonal transport and nerve degeneration, most commonly resulting in axonal sensorimotor neuropathy characterized by paresthesias and weakness (Ibrahim & Ehrlich, 2020).
  - (6) Vincristine can increase neural excitability by affecting calcium homeostasis and the dorsal root ganglia membrane (Ibrahim & Ehrlich, 2020).
  - (7) Pain in the hands and feet is often the first sign of neurotoxicity (Zajackowska et al., 2019).
  - (8) Rarely, vincristine also may cause focal neuropathies of the cranial nerves, resulting in hoarseness, diplopia, jaw pain, and facial palsies.
  - (9) Autonomic neuropathies rarely occur but can include urinary retention, orthostatic hypotension, and hypertension.
  - (10) Another rare but notable effect of vincristine specifically is its ability to cause an asymptomatic carrier of Charcot-Marie-Tooth disease to develop severe weakness and other symptoms (Kissoon et al., 2019; Zajackowska et al., 2019).
- b) Platinum-based agents*
- (1) Cisplatin and oxaliplatin are two widely used neurotoxic agents.
    - (a) PN seen with cisplatin is dose dependent and usually manifests at cumulative doses of 500–600 mg/m<sup>2</sup> (Zajackowska et al., 2019).
    - (b) Symptom severity is also dose dependent and can include numbness, tingling, and pain in the extremities.
    - (c) Additional neurotoxicity may present as myelotoxicity, nephrotoxicity, ototoxicity (e.g., tinnitus, hearing loss), and encephalopathy caused by seizures and focal neurologic deficits (Dietrich, 2020; Pellacani & Eleftheriou, 2020).
  - (2) Oxaliplatin induces a PN as two clinically distinct syndromes.
    - (a) Acute transient paresthesia in the distal extremities usually occurs within the early phase of drug administration, during or just following infusion in approximately 65%–98% of those treated (Zajackowska et al., 2019).
    - (b) A unique effect of oxaliplatin treatment is cold-triggered hand and foot paresthesias, which usually occur within a week after the first infusion and may reappear with subsequent infusions (Pellacani & Eleftheriou, 2020; Zajackowska et al., 2019).
    - (c) Other symptoms include pharyngolaryngeal dysesthesias, jaw spasms, and muscle cramps in the extremities (Pellacani & Eleftheriou, 2020; Zajackowska et al., 2019).
    - (d) Chronic cumulative sensory neuropathy can be observed in 50%–70% of those treated with oxaliplatin because of the damage caused to the sensory nerve axons (Pellacani & Eleftheriou, 2020; Zajackowska et al., 2019).
    - (e) These neuropathies cause more persistent clinical impairments, including eye and jaw pain, ptosis, visual impairment, voice changes, sensory ataxia, and muscle cramps that may persist for several months (Pellacani & Eleftheriou, 2020; Zajackowska et al., 2019).
    - (f) A frequent side effect of oxaliplatin is ocular toxicity, occurring acutely during infusion or as a late effect. Symptoms include tearing, dry eyes, conjunctivitis, blurred vision, photosensitivity, altered color vision, and eye pain triggered by cold (Cidon & Alonso, 2016; Pellacani & Eleftheriou, 2020).
- c) Taxanes*
- (1) Cabazitaxel, docetaxel, nab-paclitaxel, and paclitaxel are associated with sensory neuropathies involving the feet and occasionally the hands, with painful paresthesias, numbness, dysesthesias, dexterity deficits in toes and fingers, and altered proprioception (Ibrahim & Ehrlich, 2020; Zajackowska et al., 2019).
  - (2) Symptoms are dose dependent and usually start after the first dose and improve

after treatment discontinuation; however, symptoms may persist (Zajackowska et al., 2019).

- (3) Symptoms associated with changes in autonomic function are rarer but must be carefully evaluated in patients receiving taxanes; cardiac and vascular dysfunction reported as arrhythmias and orthostatic hypotension can occur in patients receiving paclitaxel (Dietrich, 2020).

d) Antitumor antibiotics

- (1) Of note, antitumor antibiotics (e.g., bleomycin, doxorubicin) produce highly selective neurotoxic effects (to dorsal root ganglia) and peripheral neurotoxicity.
- (2) CNS toxicity is primarily described in terms of cognitive impairment (Kesler & Blayney, 2016; Pellacani & Eleftheriou, 2020).

2. Immunotherapy

a) Thalidomide and its synthetic analogs

- (1) Neurotoxic effects from thalidomide are dose dependent (Zajackowska et al., 2019).
- (2) The most common toxicity seen with thalidomide and thalidomide analogs is somnolence (thalidomide was first marketed as a sedative).
- (3) At typical doses, approximately 50% of patients taking thalidomide develop PN (10% with severe symptoms), including distal paresthesias or dysesthesias with or without sensory loss (Ibrahim & Ehrlich, 2020; Stone & DeAngelis, 2016; Zajackowska et al., 2019).
- (4) This loss primarily occurs due to thalidomide's antiangiogenic effects, which promote peripheral vasculature loss (Ibrahim & Ehrlich, 2020).
- (5) Anti-inflammatory effects are also typical of thalidomide and even more pronounced with second-generation immunomodulatory agents, such as lenalidomide and pomalidomide (Ibrahim & Ehrlich, 2020).
- (6) Autonomic neuropathies include constipation and, rarely, impotence and bradycardia (Pellacani & Eleftheriou, 2020; Stone & DeAngelis, 2016).

b) CAR T cells

- (1) CAR T cells are manufactured using T cells drawn from the patient's blood. The T cells are then genetically modified to express a CAR specific to an antigen expressed by the patient's cancer cells.

- (2) The binding of CAR T cells to cancer antigens in the body results in T-cell proliferation and expansion and further immune activation, including elevations in cytokines, ultimately resulting in cancer cell death (Latchford & Tierney, 2020).

- (3) Neurotoxicity from CAR T cells is primarily a secondary result of cytokine-associated toxicity, also known as cytokine release syndrome.

- (4) Specific to CAR T-cell therapy, cytokine release syndrome-related neuropathies are referred to as immune effector cell-associated neurotoxicity syndrome (ICANS) (Dietrich, 2020; Harrison et al., 2020; Ridgeway et al., 2020).

- (5) ICANS symptoms are generally grouped in early and late phases.

(a) The early-phase symptoms are typical of cytokine release syndrome, usually occur within five days, and are characterized by fever and hypotension (Ridgeway et al., 2020).

(b) The late phase occurs after that and describes the general resolution of the early-phase symptoms (Ridgeway et al., 2020).

(c) This phase can typically last up to 14 days after the CAR T-cell infusion (Brudno & Kochenderfer, 2019).

- (6) Other more severe symptoms caused by ICANS are generally a result of capillary leak and primarily present as encephalopathic-type symptoms.

- (7) These symptoms result from a distinct syndrome of ICANS known as CAR T-cell-related-encephalopathy syndrome. They include headache, mental status changes, confusion, delirium, focal deficits, word-finding difficulty or aphasia, hallucinations, tremor, dysmetria, altered gait, and seizures (Brudno & Kochenderfer, 2019; Harrison et al., 2020; Kotch et al., 2019; Ridgeway et al., 2020).

- (8) Clinical management is dependent on the severity and type of presenting symptoms and can include supportive care and steroids (Ridgeway et al., 2020).

- (9) Newer evidence also suggests that tocilizumab may effectively treat cytokine release syndrome-related symptoms (Harrison et al., 2020).

c) Immune checkpoint inhibitors

- (1) Recent literature supports that immune checkpoint inhibitors also contribute

to PN complications (Chen et al., 2019; Marini et al., 2021; Möhn et al., 2019; Psimaras et al., 2019).

- (2) Most often, these complications result from specific neuropathies, including motor-sensory axonal neuropathy, demyelinating polyneuropathy, and axonal sensorimotor polyneuropathy (Chen et al., 2019; Marini et al., 2021; Möhn et al., 2019; Psimaras et al., 2019).
- (3) Another common side effect of immune checkpoint inhibitor therapy includes Guillain-Barré syndrome (Möhn et al., 2019). Patients with immune checkpoint inhibitor-induced Guillain-Barré syndrome often present with an elevated cerebrospinal fluid cell count (B. Hu et al., 2017).

#### G. Risk factors and prophylaxis

##### 1. Risk factors

- a) The clinical sequelae of neurotoxicity from antineoplastic therapies are complex functions of dose, mode of administration, exposure time, and the unique genetic susceptibilities of patients.
- b) Risk factors for the development of PN include preexisting neuropathies due to diabetes, alcohol use disorder, folate/vitamin B<sub>12</sub> deficiency, moderate obesity, hereditary sensorimotor neuropathy (e.g., Charcot-Marie-Tooth disease), or neuropathies caused by the malignancy (L.-Y. Hu et al., 2019; Ibrahim & Ehrlich, 2020; Molassiotis et al., 2019; Timmins et al., 2021).

##### 2. Prophylaxis

- a) Only a few prophylactic agents have been supported in the literature to reduce specific neurotoxic effects.
- b) Treatments such as amifostine, glutathione, infusions of calcium, magnesium, and venlafaxine have shown limited but promising results (L.-Y. Hu et al., 2019; Ibrahim & Ehrlich, 2020; Taillibert et al., 2016).
- c) Erythropoietin and lithium are newer agents of interest in recent literature but need further investigation in humans (L.-Y. Hu et al., 2019; Ibrahim & Ehrlich, 2020).
- d) Conflicting evidence supports vitamin E supplementation as an effective neuroprotective agent (L.-Y. Hu et al., 2019; Ibrahim & Ehrlich, 2020; Taillibert et al., 2016).
- e) For specific neurotoxic effects, the following have demonstrated efficacy:
  - (1) Aseptic meningitis: Prophylactic dosing with dexamethasone prior to intrathecal

chemotherapy may help reduce the risk of aseptic meningitis (Dietrich, 2020).

- (2) Seizures: For agents with known seizure risk (e.g., busulfan), prophylaxis with anti-convulsants is highly effective in reducing the development of seizures (Akiyama et al., 2018).
- (3) Autonomic neuropathy affecting gastrointestinal motility: Prevention of functional bowel disorders, such as paralytic ileus, often requires concomitant bowel prophylaxis with high fiber intake, fluid balance, and the use of opioid-sparing analgesia, stool softeners, and laxatives (Taillibert et al., 2016).
- (4) General PN: Increased physical activity and exercise have been shown to consistently mitigate the general effects of PN during treatment with antineoplastics (Duregon et al., 2018; Timmins et al., 2021). Newer evidence has shown promise for using the mitochondrial protectant pifithrin- $\mu$  in the prevention of neuropathic pain often caused by cisplatin and paclitaxel therapies (Ma et al., 2018).

#### H. Cognitive impairment

##### 1. Overview

- a) Cognitive function is a multidimensional concept that encompasses several domains regulated by the brain (e.g., attention and concentration, executive function, information processing speed, language, psychomotor ability, visuospatial skill, learning, memory) (Jansen et al., 2019; see Figure 24-1).
- b) Cognitive impairment is a decline in function in one or multiple domains of cognitive function. It may represent a single, highly specific deficit or a cluster of related deficits (Jansen et al., 2019).

##### 2. Pathophysiology

- a) Altered brain functioning and cognitive impairment: Evidence of altered brain functioning and cognitive impairment has been found prior to treatment for non-CNS cancers, indicating that cancer and tumor burden may contribute to cognitive concerns (Mayo, Lustberg, et al., 2021).
- b) Multimodal therapy: Although cancer therapies (e.g., surgery, radiation therapy, chemotherapy, targeted therapy, hematopoietic stem cell transplant, endocrine therapy, immunotherapy) have been associated with cognitive changes, the use of multimodal therapy makes it difficult to determine the underlying mechanism for cognitive impairment. Likewise, the mechanisms of cancer treatment-related cognitive changes are

thought to be multifactorial and are still not fully understood.

(1) Structural and functional damage to the brain

(a) The effects of direct tumor involvement in the brain, surgical removal of CNS tumors, or brain metastases are specific to the area of the tumor location, type of cancer, size, and rate of growth (Chang et al., 2019; Ouyang & Kanekar, 2021; Phillips et al., 2021).

(b) Structural and functional damage may also occur in patients with non-CNS cancers who receive chemotherapy, as evidenced by declines in gray matter volume (most often in the prefrontal lobe and hippocampus) and widespread decreases in white matter integrity and brain activity (Amidi & Wu, 2019).

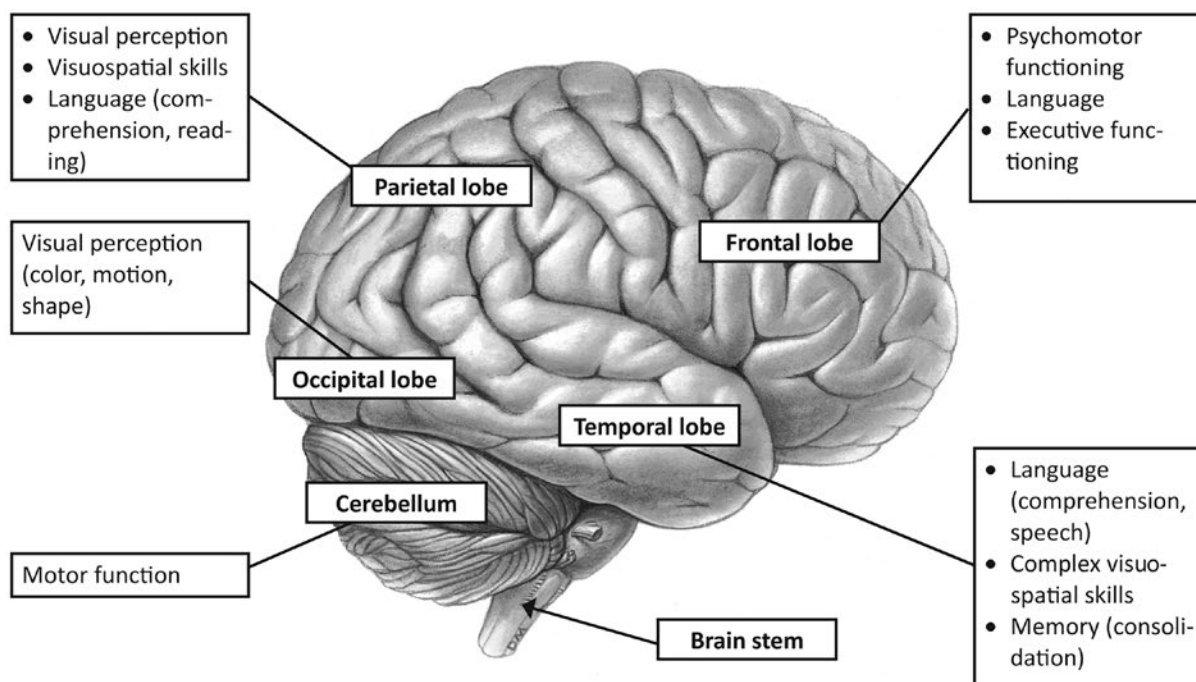
(2) Direct injury to neurons or other brain structures, including oligodendrocytes, astrocytes, glial cells, and white matter tracts

(a) Neurotoxic effects of chemotherapy may disrupt neural stem and progenitor cells within the CNS, which appear to be more sensitive than cancer cells to various chemotherapy agents (Gibson & Monje, 2019; Nguyen & Ehrlich, 2020).

(b) Specific chemotherapy drugs shown to target neural progenitor cells in experimental studies include, but are not limited to, carmustine, cisplatin, cyclophosphamide, cytarabine, docetaxel, doxorubicin, 5-fluorouracil, ixabepilone, methotrexate, paclitaxel, tamoxifen, temozolomide, thiotepa, vinblastine, and vincristine (Mounier et al., 2020; Nguyen & Ehrlich, 2020).

c) Disruption of the blood–brain barrier: Although most chemotherapy drugs are unable to cross the blood–brain barrier, antineoplastic agents cause peripheral damage to blood vessels, resulting in a disruption of blood–brain barrier integrity and adversely affecting the brain and cognitive func-

**FIGURE 24-1.** Anatomic Correlates of Cognitive Function



Note. Based on information from Bastian & Lisberger, 2021; Gazzaniga et al., 2019; Theibert, 2020.

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From "Cognitive Changes," by C. Jansen in J. Eggert (Ed.), *Cancer Basics* (2nd ed., p. 384), 2017, Oncology Nursing Society. Copyright 2017 by Oncology Nursing Society. Adapted with permission.



tioning (Fernandez et al., 2020; Mounier et al., 2020).

d) DNA damage: Several chemotherapy agents can cause DNA damage (e.g., alkylating agents), impair DNA synthesis (e.g., antimetabolites), or otherwise block DNA production (e.g., taxanes). They also may cause direct inflammatory effects, oxidative stress, and increased free radical formation, which can cause neuronal death (Nguyen & Ehrlich, 2020).

e) Cytokine dysregulation

- (1) Although many chemotherapy agents cannot cross the blood–brain barrier, they can stimulate a release of proinflammatory cytokines (e.g., interleukin-1, interleukin-6, tumor necrosis factor- $\alpha$ ) in response to cell injury.
- (2) Cytokines are proteins that have a role in neural function and repair and the metabolism of neurotransmitters.
- (3) Increased levels of cytokines may activate a stress cascade, leading to an elevation in circulating tumor necrosis factor- $\alpha$ . This can cross the blood–brain barrier and cause excessive levels of cytokines in the CNS, leading to cognitive changes (Castel et al., 2017; Shi et al., 2019).
- (4) Evidence for increased cytokine levels exists for most treatment modalities (e.g., chemotherapy, immunotherapy, radiation therapy), which can lead to declines in memory and global cognition (Williams et al., 2018).

f) Oxidative stress or inflammatory responses

- (1) Radiation therapy and chemotherapy can cause oxidative damage (Mayo, Lustberg, et al., 2021).
- (2) Various chemotherapy drugs (e.g., carboplatin, carmustine, cyclophosphamide, cytarabine, doxorubicin, methotrexate, oxaliplatin) have been shown to initiate oxidative stress that can trigger cell membrane damage and produce large amounts of free radicals (Bagnall-Moreau et al., 2019; Branca et al., 2018; Mounier et al., 2020).

g) Anemia

- (1) Primary or metastatic cancer involvement of the bone marrow or bones and cancer treatments (e.g., radiation therapy, chemotherapy) can cause anemia.
- (2) Insufficient brain oxygenation is associated with cognitive problems in multiple domains, such as attention and concentration, executive functioning, motor

function, and memory (Lezak et al., 2012; Mounier et al., 2020).

h) Hormone-mediated effects

- (1) Estrogen and androgen are neuroprotective, and receptors for these hormones are widely distributed throughout the brain (Lobo, 2019; Ryan et al., 2020; Wu & Amidi, 2017).
- (2) Although hormone agents work by different mechanisms, selective estrogen receptor modulators act as estrogen agonists or estrogen antagonists, which block estrogen receptors; aromatase inhibitors decrease estrogen synthesis in the peripheral tissues; and androgen deprivation therapy reduces testosterone levels. Their use can affect cognitive functioning (Hong et al., 2020; Ryan et al., 2020; Underwood et al., 2018; Wu & Amidi, 2017).
- (3) Greater menopausal symptoms, cognitive complaints, and slower information processing speed have been found in postmenopausal women with cancer than in healthy women (Vega et al., 2018).
- (4) Chemotherapy often induces menopause with a more accelerated decline in estrogen levels, but the significance as applied to cognitive functioning is still unclear (Lobo, 2019).
- (5) Similarly, although age-related decreases in testosterone may be associated with cognitive decline, the evidence for cognitive impairment from androgen deprivation therapies is inconsistent (Morgans et al., 2021).

i) Leukoencephalopathy

- (1) Structural alterations in cerebral white matter can occur with cranial irradiation (Phillips et al., 2021).
- (2) White matter changes have also been reported with various chemotherapy, immunotherapy, and targeted agents, such as alemtuzumab, bevacizumab, carmustine, cisplatin, cytarabine, 5-fluorouracil, fludarabine, ifosfamide, infliximab, interferon- $\alpha$ , interleukin-2, lenalidomide, levamisole, melphalan, methotrexate, rituximab, sorafenib, sunitinib, temozolomide, and thiotepa (Fernandez-Robles et al., 2016; Filley et al., 2017; Ouyang & Kanekar, 2021; Westin et al., 2018).

j) Accelerated aging

- (1) Various processes have been determined to contribute to aging (e.g., telomere attrition, cellular senescence, free radical gen-

- eration, stem cell exhaustion, increased DNA damage, epigenetic alterations) that may be associated with declines in cognitive functioning (Carroll et al., 2019; Cupit-Link et al., 2017; Wang et al., 2021).
- (2) Studies have found associations between some predictors of biologic aging (e.g., telomere attrition, increased DNA damage) and cognitive impairment (Carroll et al., 2019).
  - (3) Specific treatments that may induce accelerated aging may include, but are not limited to, chemotherapy (e.g., cisplatin, cyclophosphamide, daunorubicin, docetaxel, doxorubicin, etoposide, 5-fluorouracil, hydroxyurea, irinotecan, methotrexate, mitomycin C, paclitaxel, temozolomide, vinblastine, vincristine, vinorelbine), hormone therapy (e.g., tamoxifen), targeted therapy (e.g., dasatinib, sunitinib, vemurafenib), and radiation therapy (Cupit-Link et al., 2017).
    - (a) The incidence of treatment-related cognitive changes is difficult to determine because many factors influence cognition. However, an estimated 30%–40% of people with non-CNS cancers have cognitive impairment prior to treatment, and up to 75% have cognitive changes during or after cancer treatment (Mayo, Lustberg, et al., 2021).
    - (b) The incidence of cognitive impairment is even greater for patients undergoing hematopoietic stem cell transplantation (50%). It is as high as 40% six years after treatment (Mayo, Wozniczka, et al., 2021; Nakamura et al., 2021).
    - (c) Cognitive problems, especially difficulties with attention, concentration, memory, ability to multitask, and maintain work productivity, can persist for months or several years and are a major concern to cancer survivors, especially when reentering the workplace (Klaver et al., 2020; Von Ah et al., 2018).
    - (d) Studies have confirmed that cognitive issues continue to negatively impact survivors in the workplace for at least one if not many years after treatment (Cheng et al., 2018; Dorland et al., 2018; Klaver et al., 2020; Lange et al., 2019; Von Ah et al., 2018).
3. Risk factors: Predisposing factors that influence cognitive function are inconsistent, but the following have been suggested:
    - a) Individual risk factors
      - (1) Age: Cognitive decline occurs with aging. Although younger patients with cancer report more cognitive problems, older patients perform even worse on objective tests (Gutenkunst et al., 2021). Of note, normative data for neuropsychological tests are based on age.
      - (2) Comorbidities: Patients with greater comorbidity levels, especially illnesses such as diabetes and cardiovascular disease, have been reported to have cognitive impairment prior to initiating cancer treatments (Allen et al., 2018).
      - (3) Genetics and epigenetics
        - (a) As is the case with other treatment side effects, not all patients are equally affected by the same regimen.
        - (b) The most commonly studied genetic variants implicated in cancer treatment-related cognition include apolipoprotein E epsilon 4 variant, brain-derived neurotrophic factor, and catechol-o-methyltransferase (Buskbjerg et al., 2019; Correa et al., 2019; Demby et al., 2020; Fernandez et al., 2020; Lange et al., 2019; Li et al., 2020; Speidell et al., 2019; Tan et al., 2019; Toh et al., 2018).
        - (c) Genetic polymorphisms have become an area of increasing interest in how they might influence the individual risk of cognitive changes during a cancer diagnosis and treatment (Bender et al., 2018; Merriman et al., 2019).
    - (4) Psychological factors: Stress, anxiety, depression, and other factors can affect performance on neuropsychological testing (Lezak et al., 2012).
      - (a) Higher anxiety and depressive symptoms prior to treatment may be predictive of cognitive decline in attention, executive functioning, and memory, as measured by objective neuropsychological tests. They may also be associated with persistent cognitive problems over time (Janelins et al., 2018; Merriman et al., 2019).
      - (b) It has also been suggested that patient perception of cognitive impairment may indicate emotional distress



- (e.g., anxiety, depression, stress) and is often correlated with subjective measures of cognitive functioning (Boscher et al., 2020; Gutenkunst et al., 2021).
- (c) Unsurprisingly, higher depressive symptoms have been associated with more significant cognitive issues for survivors in the workplace (Dorland et al., 2018).
- (5) Fatigue and sleep disturbances
- (a) Fatigue can negatively affect cognitive function and is related to greater cognitive complaints during treatment and for cancer survivors (Gutenkunst et al., 2021).
- (b) Similarly, sleep disturbances (e.g., insomnia) are negatively correlated with subjective cognitive impairment (Boscher et al., 2020; Lange et al., 2019; Liou et al., 2019).
- b) Risk factors related to cancer treatments
- (1) Regimens: Because most patients receive multimodal therapy, it is difficult to determine if specific drugs or regimens promote a greater incidence of cognitive changes.
- (2) Dose intensity and cumulative effects
- (a) Cognitive changes in patients who receive cranial irradiation are related to the total dose received (Chang et al., 2019; Ouyang & Kanekar, 2021).
- (b) Exposure to higher doses of chemotherapy (or higher concentrations due to impaired clearance) and the additive or synergistic effects of multiagent regimens also may increase risk (Mounier et al., 2020).
- (c) In addition, cumulative chemotherapy cycles have been reported as a predictor of cognitive decline (Gutenkunst et al., 2021).
- (d) Similarly, decreases in cognition have been shown in women on endocrine therapy (Underwood et al., 2019).
- (3) Concomitant medications, such as analgesics, antidepressants, antiepileptics, anxiolytics, antipsychotics, immunosuppressants, and steroids, also may contribute to cognitive deficits (Jansen, 2017).
4. Clinical manifestations
- a) Although cognitive changes may be subtle, patients report difficulties with their ability to concentrate, think clearly, retain or learn new information, be efficient, organize and prioritize, manage responsibility, interact socially, and cope with problems.
- b) Cognitive problems can persist for months up to several years and are a major concern for cancer survivors, especially when reentering the workplace (Klaver et al., 2020; Von Ah et al., 2018).
5. Assessment
- a) Patients who report cognitive problems should be screened for potentially reversible factors that may contribute to cognitive impairment (Allen et al., 2018; NCCN, 2022b).
- b) Many neuropsychological tests are available to measure cognitive function but are generally used only in studies and require referral to a neuropsychologist.
- c) Imaging studies (e.g., MRI, electroencephalogram, positron-emission tomography) have been used to study electrophysiologic outcomes, synaptic activity, and structural and functional brain changes related to cognitive impairment; however, these are generally not considered feasible for routine cognitive evaluation (Deprez et al., 2018; Xu et al., 2020). NCCN (2022b) guidelines recommend imaging only to rule out structural abnormalities in high-risk patients or individuals with focal neurologic deficits.
- d) Assess patients for cognitive complaints, such as the inability to focus on tasks or follow instructions and difficulties with concentration, memory, and word-finding, including onset, duration, and intensity. One should also consider eliciting caregiver input regarding cognitive function.
- e) Assess for any focal neurologic deficits and refer to a physician for further workup (neuroimaging).
- f) Assess social history (e.g., living situation, lifestyle factors including alcohol or drug use, work history) and potential influencing factors (e.g., anxiety, depression, emotional distress, pain, sleep disturbances, fatigue). Manage any contributing symptoms.
- g) Review cancer and treatment history (e.g., tumor type, staging, treatments, disease trajectory).
- h) Review coexisting medical conditions (e.g., cardiovascular disease, diabetes, neurologic conditions, psychiatric illness) and menopausal status.
- i) Review current medications (e.g., analgesics, antidepressants, antiemetics, antiepileptics, antipsychotics, immunosuppressants, steroids); evaluate for new medications, supplements, or potential medication interactions; and adjust regimens as needed.
- j) Monitor laboratory results to determine if patients have anemia, metabolic abnormalities, new-onset endocrinopathy (e.g.,

thyroid-stimulating hormone), vitamin deficiencies (e.g., B<sub>12</sub>), or liver or renal dysfunction. Take appropriate action as indicated.

k) Consider referral for neuropsychological testing, if indicated.

#### 6. Collaborative management

a) Currently, the only evidence-based recommendation for preventing or treating cognitive impairment is cognitive training (Jansen et al., 2019; Mayo, Lustberg, et al., 2021). Although the mechanisms of cancer treatment-related cognitive changes are still unclear, several pharmacologic and nonpharmacologic interventions have been studied. Many focus on preventing cognitive impairment by targeting the potential mechanisms discussed earlier. Further research is needed to determine potential interventions for patients experiencing cognitive impairments.

#### b) Nonpharmacologic interventions

(1) Cognitive rehabilitation, which encompasses cognitive training and cognitive behavioral interventions, is the technique most likely to improve cognitive functioning.

(a) Cognitive training involves interventions to improve, maintain, or restore attention, concentration, and memory through repeated and structured practice of tasks.

(b) Cognitive behavioral interventions focus on adaptive strategies to compensate for cognitive impairment.

(c) Systematic reviews have suggested that although cognitive rehabilitation has demonstrated beneficial outcomes in several cognitive domains (e.g., memory, executive function, progressing speed), further studies are needed to ascertain the optimal delivery method, feasibility, and specific recommendations (Fernandes et al., 2019; Von Ah & Crouch, 2020).

(2) Exercise (e.g., aerobic, resistance training, yoga) was shown as potentially preventive for cognitive impairment in animal studies (Park et al., 2018).

(a) Overall, increasing evidence supports exercise as an intervention for cognitive impairment, and it is recommended in NCCN guidelines (Campbell et al., 2020; NCCN, 2022b).

(b) Future studies are needed to determine the specific types of exercise

(as well as frequency and duration) that are beneficial to preventing and improving cognitive functioning.

#### (3) Complementary interventions

(a) Complementary interventions (e.g., acupuncture, guided imagery, meditation, mindfulness, natural restorative environment, neurofeedback, nutrition) have also been studied to minimize cognitive impairment.

(b) For example, acupuncture has been used for other chemotherapy-related toxicities (e.g., PN, nausea, pain).

(c) Preliminary study results indicated that acupuncture may improve objective and subjective cognitive functioning (Tong et al., 2018; Zeng et al., 2018; Zhang et al., 2020).

(d) Evidence for other alternative therapies is even more limited.

#### c) Pharmacologic interventions

(1) Pharmacologic interventions, such as psychostimulants (e.g., methylphenidate, dexamethylphenidate, modafinil), cholinesterase inhibitors (e.g., donepezil), N-methyl-D-aspartate (NMDA) receptor antagonists (e.g., memantine), complementary medicines (e.g., ginkgo biloba, vitamin E), and erythropoiesis-stimulating agents (e.g., erythropoietin) have been evaluated; however, limited data are available to recommend their use (Jansen et al., 2019; Karschnia et al., 2019; Mayo, Lustberg, et al., 2021; Miladi et al., 2019).

(2) In fact, erythropoiesis-stimulating agents are not recommended for practice because of U.S. Food and Drug Administration warnings regarding risks associated with their use (Jansen et al., 2019).

(3) However, NCCN guidelines propose that trial use of psychostimulants may be considered for select individuals (NCCN, 2022b).

### I. Patient and family education

1. Teach patients and caregivers the general signs and symptoms of neurotoxicity and provide written information describing the immediate and delayed effects of specific treatment agents. Provide information on how, when, and to whom signs and symptoms should be reported.

2. Teach patients and caregivers to recognize signs and symptoms that may indicate life-threatening toxicities.

ties (e.g., cerebrovascular events) and instruct them to immediately seek medical attention (Banach et al., 2016).

3. When neurotoxic effects manifest, orient patients and caregivers to the relevant safety issues and precautions.

a) Seizures

- (1) Patients with a known seizure event or who are prophylactically treated for seizures should be instructed not to drive, operate heavy machinery, swim, take baths (showers only), or use heated appliances while alone (e.g., stoves, curling irons, barbecue grills).
- (2) A medical alert bracelet or similar disclosure tool should be worn or carried at all times.
- (3) Caregivers should ensure patients are in the safest position possible if a seizure does occur.
- (4) This would include lowering patients to the floor, moving objects out of the way, and not touching patients who are seizing (American Cancer Society [ACS], 2020c).

b) Sensory neuropathy

- (1) Patients with loss of sensation in their extremities are at risk for thermal or ischemic injuries.
- (2) Teach patients and caregivers to pay particular attention to hands and feet, including regular inspection of the feet, and emphasize the importance of wearing properly fitted shoes covering the entire foot (ACS, 2021).
- (3) Additionally, cold pain is a frequent symptom of neuropathic pain, manifesting as a pain response to a normally innocuous cold stimulus (cold allodynia) or heightened sensitivity to a painful cold stimulus (cold hyperalgesia).
- (4) When these symptoms are present, patients should be taught to avoid exposure to cold environments and objects and to wear gloves in low temperatures (ACS, 2021; Banach et al., 2016).

c) Motor neuropathy

- (1) Patient counseling should focus on strategies to avoid falls and injury, especially when navigating changing surfaces, such as going from a bare floor to a carpet.
- (2) Patients should consider walking shoes, which provide traction and support, and should generally opt for shoes that tie versus those that slip on (e.g., flip-flops, sandals, slippers).

- (3) Removing throw rugs, clearing walkways of clutter, and using skid strips on slippery surfaces (e.g., shower and tub floors) can help reduce the risk of falls.

- (4) When possible, patients should be offered physical or occupational therapy to preserve function and limit further injury, especially if their condition becomes chronic (ACS, 2021).

d) Autonomic neuropathy: Teach strategies to manage symptoms of autonomic dysfunction (e.g., postural hypotension, constipation, urinary retention), such as dangling the legs prior to standing, increasing oral intake, and adding dietary fiber or a formalized bowel regimen.

4. Cognitive impairment: Inform patients that cognitive changes are a possible side effect of treatment and that studies elucidating this phenomenon, its mechanisms, and subsequent interventions are ongoing (ACS, 2020a).

a) Acknowledge, validate, and record patient reports of cognitive changes.

b) Encourage patients and family members to report cognitive problems.

c) Acknowledge that although studies have been done for various interventions, limited evidence is available to make treatment recommendations.

d) Encourage routine physical activity.

e) Recommend optimizing management of anxiety, depression, fatigue, sleep disturbances, and other contributing symptoms (NCCN, 2022b).

f) If patients show signs of confusion or delirium, they or their caregivers should call their provider immediately (ACS, 2020b).

g) General management strategies have been suggested (ACS, 2021; NCCN, 2022b).

(1) Healthy lifestyle practices

(a) Ensure adequate sleep and rest.

(b) Eat a well-balanced diet.

(c) Engage in physical exercise.

(2) Intellectual activities (e.g., reading, learning new skills, solving puzzles, working out math problems)

(3) Social activities (e.g., support groups)

(4) Practical management

(a) Use technology (e.g., smartphones, voice recorders).

(b) Keep a daily planner or calendar.

(c) Keep things in the same place.

(d) Develop lists, write reminders, and use notes.

(e) Reduce distractions and focus on one task at a time.

(f) Develop a routine schedule.

(5) Work strategies (Klaver et al., 2020)

- (a) Accept limitations.
- (b) Split assignments into manageable subtasks.
- (c) Decrease work hours and purposively take breaks.

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## CHAPTER 25

# Ocular Toxicities

### A. Overview

1. Patients may develop ocular toxicities due to cancer treatments, with the onset, presentation, and incidence varying by drug and dose.
2. Nurses should be familiar with the signs and symptoms, assessment, and management of these potential complications. Patients receiving novel therapies, such as targeted therapies and immune checkpoint inhibitors, should complete ophthalmologic examinations at baseline (Bindiganavile et al., 2021; Corbelli et al., 2019; Dolgin, 2020; Fortes et al., 2021; Fu et al., 2017; Kunkler et al., 2019; Liu et al., 2020; Montazeri & Bellmunt, 2020; National Cancer Institute Cancer Therapy Evaluation Program, 2017; Park et al., 2021; Schoenfeld et al., 2020; Shah & Shah, 2019; Shahzad et al., 2021; Vishnevskia-Dai et al., 2021; Young et al., 2021).
3. Patient and family education includes recognition, mechanisms for reporting, mitigation (if possible), and management strategies (Bitton et al., 2019; Davis & Francis, 2017; Fu et al., 2017; Young et al., 2021).

### B. Pathophysiology

1. The etiology of ocular toxicity is not fully understood and may include the following (see Table 25-1):
  - a) Damage to the eye or eye structures related directly to treatment, such as distribution of cytotoxic drugs in tears, direct vascular injury during intracarotid administration, direct nerve injury from chemotherapy or radiation therapy, solubility characteristics of the drug and its ability to gain access through barriers such as the blood–ocular barrier, and inflammatory toxicities related to immunotherapies (Bhatti & Salama, 2018; DeAngelis, 2017; Liu et al., 2020; Park et al., 2021; Puzanov et al., 2017)
  - b) A secondary process related to treatment, such as eye irritation caused by loss of eyelashes in the presence of neutropenia (Schoenfeld et al., 2020)
  - c) A secondary process related to concurrent diseases, such as diabetes or Graves disease leading to diplopia or ptosis (DeAngelis, 2017)
  - d) Metastases to the eyes or central nervous system resulting in increased intracranial pressure
  - e) Factors unrelated to cytotoxic therapy, such as head trauma or drug toxicity from narcotics or anticonvulsants leading to diplopia (DeAngelis, 2017)
  - f) Checkpoint inhibitors: Checkpoint inhibitors are immunologic agents that block inhibitory receptors of immune system elements, such as cytotoxic T-lymphocyte antigen 4, programmed cell death protein 1, and its ligand, leading to the activation of specific antitumor T-cell responses (Bitton et al., 2019; Emens et al., 2019; Liu et al., 2020; Park et al., 2021; Shahzad et al., 2021; Young et al., 2021).
    - (1) The mechanisms of immune-related adverse events have been hypothesized to involve a breakdown of peripheral tolerance and induction of organ-specific inflammatory processes due to their non-specific immune activation. By disrupting checkpoints to preexisting antitumor immune responses, the therapies permit the immune system to fight cancer (Bitton et al., 2019; Park et al., 2021; Young et al., 2021).
    - (2) Ophthalmic immune-related adverse events include iritis, uveitis, conjunctivitis, dry eyes, and blurred vision. These can be treated with topical nonsteroidal or steroid therapy (Bhatti & Salama, 2018; Bitton et al., 2019; Brahmer et al., 2018; Durrechou et al., 2020; Emens et al., 2019; Fortes et al., 2021; Park et al., 2021; Puzanov et al., 2017; Schoenfeld et al., 2020; Shahzad et al., 2021; Young et al., 2021).
  - g) Epidermal growth factor receptor (EGFR) inhibitors: EGFR is a normal part of epidermal cells. It is widely distributed on the eye surface in the conjunctival and corneal epithelium, as well as in the eyelid skin, lash follicles, tear glands, and seba-

**TABLE 25-1.** Ocular Toxicities and Their Treatments

| Toxicity                                        | Definition and Symptoms                                                                                                                                                                                       | Treatment                                                                                                                                                                                                       |
|-------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Blepharitis                                     | Inflammation of the eyelids, mainly at the margin<br>Redness and flaking of the skin on the eyelids and crusting that worsens on waking                                                                       | Use warm compress, eyelid hygiene, and corticosteroids or anti-inflammatory medications.                                                                                                                        |
| Blurred vision                                  | Decreased clarity or sharpness in vision                                                                                                                                                                      | Refer to an ophthalmologist.<br>Discontinue agent.                                                                                                                                                              |
| Central serous retinopathy                      | Localized serous retinal detachment observable only on fundoscopy<br>Manifests as slightly blurry vision and the perception of objects smaller than they are (micropsia)                                      | —                                                                                                                                                                                                               |
| Conjunctivitis                                  | Inflammation and redness of the conjunctiva                                                                                                                                                                   | Hold agent.<br>Use corticosteroids or anti-inflammatory medications and artificial tears.                                                                                                                       |
| Corneal edema                                   | Swelling of the cornea                                                                                                                                                                                        | Refer to an ophthalmologist.                                                                                                                                                                                    |
| Corneal epithelial defect                       | Significant eye pain, sensitivity to light                                                                                                                                                                    | Refer to an ophthalmologist.                                                                                                                                                                                    |
| Cystoid macular edema                           | Chronic inflammation of the macular area only observable on fundoscopy and confirmed by fluorescein angiography                                                                                               | Refer to an ophthalmologist.<br>Hold agent.                                                                                                                                                                     |
| Diplopia                                        | Double vision                                                                                                                                                                                                 | Refer to an ophthalmologist and neurologist.                                                                                                                                                                    |
| Dysfunctional tear syndrome (tear film changes) | Fluctuating or mild decrease in vision, transient eye pain, burning or foreign body sensation in the eye, eye fatigue                                                                                         | Mild symptoms: Apply supplemental tears 4–6 times daily.<br>Severe symptoms or no relief: Refer to an ophthalmologist. Treatment may consist of punctal plugs or anti-inflammatory medications.                 |
| Epiphora                                        | Excessive tear production, usually caused by eye irritation                                                                                                                                                   | Refer to an ophthalmologist.<br>Use topical lubricants.                                                                                                                                                         |
| Hemianopia                                      | Visual field defect that respects the vertical midline in both eyes<br>Can be homonymous or bitemporal                                                                                                        | —                                                                                                                                                                                                               |
| Iridocyclitis                                   | Sensitivity to light, sustained eye pain, decrease in vision                                                                                                                                                  | Refer to an ophthalmologist.<br>Treatment involves the use of anti-inflammatory medications.                                                                                                                    |
| Keratitis and keratopathy                       | Inflammation of the cornea, usually referring to the corneal surface (epithelium)<br>Manifests as pain, photophobia, and increased lacrimation<br>More evident in slit-lamp examination with the aid of a dye | Refer to an ophthalmologist.<br>Use topical lubricants.                                                                                                                                                         |
| Lacrimal duct stenosis                          | Narrowing of the tear duct                                                                                                                                                                                    | Refer to an ophthalmologist.<br>Hold agent.                                                                                                                                                                     |
| Maculopathy                                     | Disease or damage to the central part of the retina or macula                                                                                                                                                 | Refer to an ophthalmologist.<br>Discontinue agent.                                                                                                                                                              |
| Meibomitis (meibomian gland dysfunction)        | Fluctuations in vision (varying degrees), burning sensation in the eye, some mucous discharge, eye redness (may occur only on awakening)                                                                      | Clean eyelid and apply warm compresses to the eyelid for at least 4 minutes twice daily. Use artificial lubricants.<br>If lid scrubs and warm compresses are ineffective, consider topical or oral antibiotics. |
| Optic neuritis                                  | Inflammation of the optic nerve                                                                                                                                                                               | Refer to an ophthalmologist and neurologist.<br>Discontinue agent.                                                                                                                                              |

(Continued on next page)

**TABLE 25-1.** Ocular Toxicities and Their Treatments (*Continued*)

| Toxicity                                         | Definition and Symptoms                                                                                                                                                                                                           | Treatment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|--------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Papilledema                                      | Optic disc swelling caused by increased intracranial pressure                                                                                                                                                                     | Use corticosteroids or anti-inflammatory medications.<br>Discontinue agent.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Periorbital edema                                | Inflammation and increased fluid accumulation of the interstitial tissues from the eyelid into the orbital septum<br>Manifests as a hard swelling of the eyelid                                                                   | Apply warm compress.<br>Refer to an ophthalmologist.<br>Discontinue agent.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Periorbital rash                                 | Discoloration of the tissue around the eye                                                                                                                                                                                        | Use corticosteroids or anti-inflammatory medications, warm compress, and eyelid hygiene.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Photopsia and photophobia                        | Ocular pain and sensitivity to light                                                                                                                                                                                              | Use topical lubricants.<br>Avoid light exposure.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Ptosis                                           | Drooping or falling of the upper eyelid over the eye<br>Also known as drooping eyes                                                                                                                                               | Refer to an ophthalmologist and neurologist.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Retinal vein occlusion                           | Blockage of the small veins that carry blood away from the retina                                                                                                                                                                 | Refer to an ophthalmologist.<br>Discontinue agent.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Retinopathy                                      | Damage to the retina caused by abnormal blood flow                                                                                                                                                                                | Refer to an ophthalmologist and neurologist.<br>Discontinue agent.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Squamous blepharitis (i.e., eyelid skin changes) | Hyperemia, papulopustular rash, crusting<br>Sore and irritated eyelids, with discomfort described as severe<br>Mild redness to significant edema and soreness of the eyelid margin<br>Small pustules at the base of the eyelashes | Acute reactions: Apply warm compresses with a moist washcloth; ensure regular cleaning of the eyelid; use an artificial lubricant.<br>Apply fluorometholone (0.1%) ointment to the eyelid (both skin and lid margin) for 1 week. Do not use for > 2 weeks. An ophthalmologist must examine the patient within 4 weeks.<br>Chronic reactions: Apply tacrolimus 0.03% ointment or pimecrolimus cream twice daily to the skin of the eyelid only. If treatment is minimally effective or not effective at all, try tacrolimus 0.1%. This treatment should not be used for > 6 months. |
| Trichomegaly                                     | Pathologically long eyelashes that can get misdirected and cause ocular surface abrasions                                                                                                                                         | Refer to an ophthalmologist.<br>Trim long or misdirected eyelashes.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Uveitis                                          | Inflammation of the uveal tract; can be anterior (involving the anterior chamber and iris) or posterior (involving the vitreous and choroid)                                                                                      | Refer to an ophthalmologist.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

*Note.* Based on information from Bhatti & Salama, 2018; Bindiganavile et al., 2021; Bitton et al., 2019; Brahmer et al., 2018; Chelala et al., 2019; Corbelli et al., 2019; Davis & Francis, 2017; Dolgin, 2020; Durrechou et al., 2020; Emens et al., 2019; Fortes et al., 2021; Fu et al., 2017; Kunkler et al., 2019; Liu et al., 2020; Montazeri & Bellmunt, 2020; Moshirfar et al., 2021; Munir & Aylward, 2017; National Cancer Institute Cancer Therapy Evaluation Program, 2017; Park et al., 2021; Puzanov et al., 2017; Schoenfeld et al., 2020; Shah & Shah, 2019; Shahzad et al., 2021.

ceous and sweat glands (Liu et al., 2020; Moshirfar et al., 2021; Puzanov et al., 2017; Shah & Shah, 2019). The EGFR pathway regulates proliferation and ocular tissue differentiation. Inhibiting EGFR can cause damage to the epidermal cells found in the ocular region, which includes the eye and surrounding skin (Bhatti & Salama, 2018; Fortes et al., 2021; Fu et al., 2017; Moshirfar et al., 2021).

- (1) Examples of EGFR inhibitor-induced effects are tear film dysfunction and unusual hyperpigmentation or hypopig-

mentation. EGFR inhibitors have led to dry eyes, inflammation of the lid margin (blepharitis), dysfunction of the sebaceous glands of the eyelid (meibomitis), corneal erosion, and inversion or eversion of the eyelid margin (Liu et al., 2020; Moshirfar et al., 2021; Shah & Shah, 2019).

- (2) EGFR also has a crucial role in regulating the hair growth cycle.
  - (a) An EGFR inhibitor can hinder this cycle, leading to loss of eyelashes and



eyebrows or an accelerated growth and curling of the eyelashes, leading to tortuous eyelashes or eyelash trichomegaly (Moshirfar et al., 2021).

- (b) Most ocular side effects are not vision threatening but should be followed by an ophthalmologist to quickly treat the discomfort and prevent ocular injury (Bhatti & Salama, 2018; Bitton et al., 2019; Durrechou et al., 2020; Fortes et al., 2021; Moshirfar et al., 2021; National Cancer Institute Cancer Therapy Evaluation Program, 2017; Puzanov et al., 2017; Schoenfeld et al., 2020; Shah & Shah, 2019; Shahzad et al., 2021).
  - h) B-cell maturation antigen–targeted therapies may have a specter of toxicities.
    - (1) Belantamab mafodotin, recently approved by the U.S. Food and Drug Administration to treat multiple myeloma, may produce dry eyes and blurring but can progress to keratopathy (Dolgin, 2020).
    - (2) An ophthalmic examination should be performed at baseline, prior to each dose, and promptly for worsening symptoms.
    - (3) Belantamab mafodotin should be held until improvement. Based on severity, it can be resumed or permanently discontinued (Markham, 2020).
  - i) Antibody-drug conjugates that combine a monoclonal antibody and a cytotoxic drug attachment can be directed to a specific antigen on tumors. Tisotumab vedotin, approved by the U.S. Food and Drug Administration to treat cervical cancer and graft-versus-host disease, has a black box warning specific to ocular toxicities with mitigation strategies (Seagen, 2021).
  - j) A growing number of actionable gene alterations increase the list of targeted treatments. Erdafitinib received U.S. Food and Drug Administration approval as a pan-fibroblast growth factor receptor inhibitor in 2020. Grade 3 or higher ocular toxicities caused permanent discontinuation (Montazeri & Bellmunt, 2020).
2. A broad spectrum of disorders have been documented, including the inflammatory conditions uveitis, conjunctivitis, keratitis, blepharitis, and iritis and the development of retinal opacities, cataract formation, lid and lacrimation disorders, optic neuritis, and other neurologic injuries (Bindigana-vile et al., 2021; Brahmer et al., 2018; Davis & Francis, 2017; Fortes et al., 2021; Kunkler et al., 2019; Puzanov et al., 2017). For site-specific disorders, see Table 25-2.

**TABLE 25-2.** Specific Ocular Toxicities by Anatomic Site

| Site                                 | Ocular Toxicity                                                                                     |
|--------------------------------------|-----------------------------------------------------------------------------------------------------|
| Central nervous system               | Cortical blindness, internuclear ophthalmoplegia, blepharospasm                                     |
| Conjunctiva                          | Conjunctivitis                                                                                      |
| Cornea                               | Keratopathy, keratitis                                                                              |
| Cranial nerves III, IV, V, VI        | Ptosis, paresis with or without diplopia, corneal hypesthesia                                       |
| Extraocular muscles                  | Fibrosis                                                                                            |
| Lacrimal drainage                    | Tear duct fibrosis, punctal occlusion                                                               |
| Lacrimal gland                       | Keratoconjunctivitis sicca                                                                          |
| Lens                                 | Cataract                                                                                            |
| Lids                                 | Cicatricial ectropion, ankyloblepharon, increased lid necrosis after cryotherapy, hyperpigmentation |
| Optic nerve                          | Disc edema, optic neuritis, optic atrophy                                                           |
| Orbit                                | Arteriovenous shunts, cavernous sinus syndrome, edema, exophthalmos, pallor, pain                   |
| Pupil                                | Pinpoint pupils, internal ophthalmoplegia                                                           |
| Retina                               | Toxic retinopathy                                                                                   |
| Sclera                               | Discoloration                                                                                       |
| Trabecular meshwork and ciliary body | Increased intraocular pressure                                                                      |
| Uvea                                 | Uveitis                                                                                             |
| Vitreous                             | Opacification                                                                                       |

*Note.* Based on information from Bhatti & Salama, 2018; Bindigana-vile et al., 2021; Bitton et al., 2019; Brahmer et al., 2018; Davis & Francis, 2017; Durrechou et al., 2020; Fortes et al., 2021; Fu et al., 2017; Kunkler et al., 2019; Liu et al., 2020; National Cancer Institute Cancer Therapy Evaluation Program, 2017; Park et al., 2021; Puzanov et al., 2017; Schoenfeld et al., 2020; Shahzad et al., 2021; Young et al., 2021.

3. With frequent use of combination therapy, it may be challenging to determine the specific drug causing complications.
4. Patients may experience toxicity-related visual impairment during and up to two weeks after chemotherapy (Kende et al., 1979). Neurologic damage to the eye has occurred up to 43 days following chemotherapy (Warrell & Berman, 1986).
5. The toxic effect of certain drugs may be cumulative and dose dependent.

6. Ocular changes may go unnoticed until irreversible damage occurs (Shahzad et al., 2021).
7. Ocular signs and symptoms, such as dry eyes and keratoconjunctivitis sicca, may precede the development of peripheral neuropathies and thus may be an important marker of neurologic status (Bhatti & Salama, 2018).
8. The presence of ocular signs or symptoms may predict the development of graft-versus-host disease in patients who have received an allogeneic hematopoietic stem cell transplant (Munir & Aylward, 2017).
9. Ocular changes may be incorrectly attributed to the aging process and underreported (Brahmer et al., 2018; Davis & Francis, 2017; Kunkler et al., 2019; Schoenfeld et al., 2020).

#### C. Incidence

1. Incidence varies according to drug classification, dose, and route of administration (see Table 25-3).
2. Ophthalmologic effects of chemotherapy occur less frequently and tend to be less severe than other chemotherapy-related side effects. Most ocular side effects tend to improve or even resolve completely upon discontinuation of the drug. Early detection often minimizes sequelae (Bitton et al., 2019; Kunkler et al., 2019; Schoenfeld et al., 2020).
3. Ophthalmic immune-related adverse events have been reported in 1%–3% of patients (Bhatti & Salama, 2018; Bitton et al., 2019; Durrechou et al., 2020; Shahzad et al., 2021). Ocular toxicities occur in 4%–64% of patients using EGFR tyrosine kinase inhibitors; most are grade 2 or lower (Chelala et al., 2019; Fortes et al., 2021; Fu et al., 2017; Liu et al., 2020; Montazeri & Bellmunt, 2020; Shah & Shah, 2019).

D. Risk factors: Causal relationships between agents and ocular toxicities are difficult to establish. Risk factors are equally difficult to establish.

E. Clinical manifestations: These may be noted as class-specific ocular adverse effects and should be anticipated or at least evaluated and reviewed. Most ophthalmic effects can be treated with specific ocular therapy without discontinuation of cancer treatment. Ophthalmologists are integral members of the treatment team, as they maintain a high level of suspicion regarding class effects (Fortes et al., 2021).

#### F. Assessment

1. Ask patients about a history of any eye disturbances and changes to their vision at each visit.
2. In addition, assess the following (Bickley, 2017; Brahmer et al., 2018; Davis & Francis, 2017; Durrechou et al., 2020; Fu et al., 2017; Kunkler et al., 2019; Liu

et al., 2020; Montazeri & Bellmunt, 2020; Moshirfar et al., 2021; National Cancer Institute Cancer Therapy Evaluation Program, 2017; Puzanov et al., 2017; Schoenfeld et al., 2020; Shah & Shah, 2019; Shahzad et al., 2021; Vishnevskia-Dai et al., 2021):

##### a) Visual acuity

- (1) Use a Snellen eye chart if possible.
  - (a) Position the patient 20 feet from the chart.
  - (b) Have the patient wear glasses or contacts for the examination if the corrective lenses are typically used other than for reading.
  - (c) Ask the patient to cover one eye with a card and to read the smallest line possible.
  - (d) Have the patient repeat with the other eye.

- (2) Acuity can be assessed using a near-vision card held at arm's length; patients who wear glasses or contact lenses should remove them. Record any visual disturbances.

##### b) Visual fields

- (1) Sit or stand in front of the patient and have the patient look with both eyes into your eyes.
- (2) While the patient gazes into your eyes, place your hands two feet apart, lateral to the patient's ears.
- (3) Instruct the patient to point to your fingers as soon as they are seen.
- (4) Slowly move your fingers along an imaginary bowl and toward the line of gaze until the patient identifies them.
- (5) Repeat this pattern in upper and lower temporal quadrants.

##### c) Position of eyes, eyebrows, and eyelids

- (1) While standing or sitting in front of the patient, observe the eyes for position and alignment with each other.
- (2) Inspect the eyebrows, noting their quantity and distribution and any flaking of the underlying skin.
- (3) Survey the eyelids, observing and palpating for signs of erythema and edema.
- (4) Assess for signs of exudates, crusting, and presence of ptosis.
- (5) Observe the condition of lashes.

##### d) Lacrimation: Note dryness, foreign body sensation, excessive tearing, or swelling of the lacrimal sac.

##### e) Conjunctiva and sclera

- (1) Ask the patient to look up as you depress both lower lids with your thumbs, exposing the sclera and conjunctiva.

**TABLE 25-3.** Ocular Toxicities of Antineoplastic Agents

| Classification             | Drug                                                                                | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Nursing Considerations                                                                                                                                                                                                                                                                                      |
|----------------------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Chemotherapy Agents</b> |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                             |
| Alkylating agents          | Busulfan (IV: Busulfex <sup>®</sup> ; oral: Myleran <sup>®</sup> )                  | Long-standing reports of cataract formation and blurred vision; rare cases of keratoconjunctivitis sicca                                                                                                                                                                                                                                                                                                                                                                                                                                           | Toxic effects are believed to act on proliferating lens epithelial cells.<br>(Bobba & Klein, 2012; Singh & Singh, 2012)                                                                                                                                                                                     |
|                            | Carboplatin                                                                         | IV: rare cases of blurred vision, eye pain; reports of maculopathy and optic neuropathy with transient cortical blindness when given to patients with renal dysfunction<br>Intracarotid: reports of severe ocular and orbital toxicity in ipsilateral eye following intracarotid injection                                                                                                                                                                                                                                                         | (Al-Tweigeri et al., 1996; Singh & Singh, 2012; Watanabe et al., 2002)                                                                                                                                                                                                                                      |
|                            | Chlorambucil (Leukeran <sup>®</sup> )                                               | Keratitis, diplopia, bilateral papilledema, retinal hemorrhages, oculomotor disturbance, disc edema, retinopathy                                                                                                                                                                                                                                                                                                                                                                                                                                   | Ocular toxicity is rare.<br>(Bobba & Klein, 2012)                                                                                                                                                                                                                                                           |
|                            | Cisplatin                                                                           | IV: blurred vision, altered color perception, papilledema, decreased visual acuity, retrobulbar neuritis, transient cortical blindness, disc edema, retinopathy, electroretinogram abnormalities, cavernous sinus syndrome, color blindness<br>Intracarotid: ipsilateral visual loss (15%–60%) from retinal or optic nerve ischemia, possibly prevented by infusion distal to the ophthalmic artery; optic neuropathy; unilateral vision loss; retinal pigment disturbances; altered color perception; cotton wool spots; intraretinal hemorrhages | Ocular toxicity has generally been reported after using regimens with higher doses or greater dose frequency than those recommended by the manufacturer. Improvement or total recovery usually occurs after discontinuation of cisplatin.<br>(Bobba & Klein, 2012; Kunkler et al., 2019; Kwan et al., 2006) |
|                            | Cyclophosphamide                                                                    | Blurred vision (reversible), keratoconjunctivitis sicca, pinpoint pupils                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | (Singh & Singh, 2012)                                                                                                                                                                                                                                                                                       |
|                            | Ifosfamide (Ifex <sup>®</sup> )                                                     | IV: blurred vision (reversible), conjunctivitis                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | (Bobba & Klein, 2012; Singh & Singh, 2012)                                                                                                                                                                                                                                                                  |
|                            | Mechlorethamine (nitrogen mustard; Mustargen <sup>®</sup> , Valchlor <sup>®</sup> ) | Intracarotid: rare reports of ipsilateral necrotizing uveitis and necrotizing vasculitis of choroids                                                                                                                                                                                                                                                                                                                                                                                                                                               | No reports exist of ocular toxicity with IV administration.<br>(Bobba & Klein, 2012)                                                                                                                                                                                                                        |
|                            | Oxaliplatin (Eloxatin <sup>®</sup> )                                                | Mild changes: dry eyes, excessive tearing, severe ocular irritation, conjunctivitis, abnormal lacrimation<br>Severe changes: retinal damages, visual field cuts                                                                                                                                                                                                                                                                                                                                                                                    | Look for patients complaining of blurred vision, visual loss, tunnel vision, or altered color vision. Most changes are transient and reversible once treatment is discontinued.<br>(Kunkler et al., 2019; Mesquida et al., 2010; Singh & Singh, 2012)                                                       |
| Antimetabolites            | Capecitabine (Xeloda <sup>®</sup> )                                                 | Ocular irritation, decreased vision, corneal deposits                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | (Kunkler et al., 2019; Singh & Singh, 2012; Waikhom et al., 2000)                                                                                                                                                                                                                                           |

(Continued on next page)

**TABLE 25-3.** Ocular Toxicities of Antineoplastic Agents (*Continued*)

| Classification                      | Drug                      | Side Effects                                                                                                                                                                                                                                                                                                                                                                     | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                   |
|-------------------------------------|---------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Chemotherapy Agents (Cont.)</b>  |                           |                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                          |
| Antimetabolites<br>( <i>Cont.</i> ) | Cytarabine                | IV: keratitis and conjunctivitis most common; blurred vision with evidence of bilateral conjunctival hyperemia, ocular pain, photophobia, and foreign body sensation at high doses; case reports of corneal toxicity with low dose of cytarabine<br>Intrathecal: optic neuropathy leading to severe visual loss (potentiated by cranial radiation therapy)                       | Hydrocortisone or dexamethasone eye drops may prevent keratitis. It is recommended to start eye drops the evening before therapy begins. (Bobba & Klein, 2012; Hopen et al., 1981; Lochhead et al., 2003)                                                                                                                                                                |
|                                     | 5-Fluorouracil (Adrucil®) | Conjunctivitis, excessive lacrimation; tear duct fibrosis; blepharitis<br>Other ocular toxicities: keratoconjunctivitis, cicatricial ectropion, ankyloblepharon, blepharospasm, punctal occlusion, oculomotor disturbances, blurred vision, photophobia, nystagmus, increased lid necrosis after cryotherapy, ocular pain, circumorbital edemas, dry eyes, and excessive tearing | Loprinzi et al. (1994) studied ice packs to decrease ocular irritation; effectiveness was also reinforced in a North Central Cancer Treatment Group clinical trial (ice applied for 30 minutes, starting 5 minutes before infusion).<br>The use of dexamethasone eye drops decreased ocular toxicities. (Haidak et al., 1978; Kunkler et al., 2019; Singh & Singh, 2012) |
|                                     | Fludarabine               | Decreased visual acuity (most common presenting sign before the development of progressive encephalopathy); rare cases of diplopia, photophobia, and optic neuritis                                                                                                                                                                                                              | Effects are dose dependent. (Bobba & Klein, 2012; Singh & Singh, 2012)                                                                                                                                                                                                                                                                                                   |
|                                     | Gemcitabine (Gemzar®)     | Retinopathy                                                                                                                                                                                                                                                                                                                                                                      | (Eli Lilly and Company, 2019)                                                                                                                                                                                                                                                                                                                                            |
|                                     | Methotrexate              | IV: blepharitis, conjunctival hyperemia, increased lacrimation, periorbital edema, photophobia, optic pain<br>Intrathecal: With concurrent radiation, case reports of bilateral ophthalmoplegia with exotropia; optic nerve atrophy<br>Intra-arterial: retinal changes in the ipsilateral eye                                                                                    | Up to 25% of patients may develop ocular toxicity. Toxicity is more common with higher doses.<br>The drug is found in tears. (Bobba & Klein, 2012; Singh & Singh, 2012)                                                                                                                                                                                                  |
|                                     | Pemetrexed (Alimta®)      | Conjunctivitis: generally associated with hyperemia, irritation, and serous secretions                                                                                                                                                                                                                                                                                           | Treatment usually involves artificial tears, withdrawal of the agent, and a short course of topical steroids. Treatment is usually curative. (Kunkler et al., 2019)                                                                                                                                                                                                      |
|                                     | Pentostatin (Nipent™)     | Conjunctivitis, photophobia, diplopia; abnormal vision, amblyopia, conjunctivitis, dry eyes, problems with lacrimation, photophobia, retinopathy, watery eyes                                                                                                                                                                                                                    | (Singh & Singh, 2012)                                                                                                                                                                                                                                                                                                                                                    |
| Antitumor antibiotics               | Doxorubicin (Adriamycin®) | Conjunctivitis, increased lacrimation (in up to 25% of patients receiving doxorubicin)                                                                                                                                                                                                                                                                                           | Serious ocular side effects are rare. (Bobba & Klein, 2012; Kunkler et al., 2019; Singh & Singh, 2012)                                                                                                                                                                                                                                                                   |

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**TABLE 25-3.** Ocular Toxicities of Antineoplastic Agents (*Continued*)

| Classification                         | Drug                                                                               | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                                                     | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                       |
|----------------------------------------|------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Chemotherapy Agents (Cont.)</b>     |                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Antitumor antibiotics ( <i>Cont.</i> ) | Mitomycin C (Muta-mycin <sup>®</sup> )                                             | IV: blurred vision<br>Topical: keratoconjunctivitis                                                                                                                                                                                                                                                                                                                                                                                              | Besides blurred vision, keratoconjunctivitis was reported after topical use in ophthalmologic surgeries.<br>(Bobba & Klein, 2012; Singh & Singh, 2012)                                                                                                                                                                                                                                                                       |
|                                        | Mitoxantrone                                                                       | Conjunctivitis, discoloration of the sclera                                                                                                                                                                                                                                                                                                                                                                                                      | The drug is secreted in tears.                                                                                                                                                                                                                                                                                                                                                                                               |
| Epipodophyllo-toxins                   | Etoposide (Topo-sar <sup>™</sup> ), etoposide phosphate (Etopo-phos <sup>®</sup> ) | Intracarotid: optic neuritis, transient cortical blindness                                                                                                                                                                                                                                                                                                                                                                                       | Effects occur when etoposide is given in combination with carboplatin.<br>(Lauer et al., 1999)                                                                                                                                                                                                                                                                                                                               |
| Nitrosoureas                           | Carmustine (BiCNU <sup>®</sup> ), lomustine (Gleo-stine <sup>®</sup> )             | Optic neuritis and atrophy, hyperemia, orbital pain, retinopathy, corneal opacities and edema, orbital IV shunts, secondary glaucoma, internal ophthalmoplegia, blurred vision, vitreous opacification, extraocular muscle fibrosis, diplopia<br>IV: rare reports of delayed blurred vision and loss of depth perception<br>Intracarotid: severe ipsilateral occurrences, including arterial narrowing, disc edema, and intraretinal hemorrhages | (Bobba & Klein, 2012; Singh & Singh, 2012)                                                                                                                                                                                                                                                                                                                                                                                   |
| Miscellaneous                          | Mitotane (Lysodren <sup>®</sup> )                                                  | Visual blurring, diplopia, lens opacity, toxic retinopathy                                                                                                                                                                                                                                                                                                                                                                                       | Ocular side effects are infrequent.<br>(Bristol-Myers Squibb, 2021)                                                                                                                                                                                                                                                                                                                                                          |
|                                        | Procarbazine (Matu-lane <sup>®</sup> )                                             | Retinal hemorrhage, papilledema, photophobia, diplopia, inability to focus                                                                                                                                                                                                                                                                                                                                                                       | Ophthalmic side effects are rare.<br>(Sigma-Tau Pharmaceuticals, 2008)                                                                                                                                                                                                                                                                                                                                                       |
| Taxanes                                | Docetaxel (Taxotere <sup>®</sup> )                                                 | Epiphora, canalicular stenosis, nasolacrimal duct obstruction, conjunctivitis, punctal stenosis, optic neuropathy                                                                                                                                                                                                                                                                                                                                | The drug is secreted in tears. Successful treatment is achieved with bicanalicular silicone intubation. Optic neuropathy is treated with steroids.<br>(Ahmadi & Esmaeli, 2001; Kunkler et al., 2019; Moloney et al., 2014; Singh & Singh, 2012)                                                                                                                                                                              |
|                                        | Paclitaxel (Taxol <sup>®</sup> )                                                   | Scintillating scotomas or shooting lights in 20% of cases, which resolved spontaneously; transient scintillating scotoma, visual impairment, photopsia, possible ischemic optic neuropathy, bilateral cystoid macular edema, retinal capillary leakage, intracellular fluid accumulation, glaucoma, dry eyes, keratitis                                                                                                                          | Scotomas usually occur toward the end of the 3-hour infusion. Photopsia usually appears during the last 30 minutes of the infusion and resolves within 3 hours. Toxicities are treated by discontinuing the agent and using topical carbonic anhydrase agents and injection of anti-vascular endothelial growth factor antibodies.<br>(Bobba & Klein, 2012; Kunkler et al., 2019; Rao & Choudhry, 2016; Singh & Singh, 2012) |

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**TABLE 25-3.** Ocular Toxicities of Antineoplastic Agents (*Continued*)

| Classification                     | Drug                                                                 | Side Effects                                                                                                                                                                                                                                                            | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                           |
|------------------------------------|----------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Chemotherapy Agents (Cont.)</b> |                                                                      |                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Vinca alkaloids                    | Vinblastine (Velban®)                                                | Extraocular muscle palsies, cranial nerve palsies, optic neuropathy, optic atrophy, cortical blindness, night blindness                                                                                                                                                 | (Singh & Singh, 2012)                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                    | Vincristine (Marqibo®)                                               | Cranial nerve palsies, optic neuropathy, optic atrophy, case reports of transient cortical blindness, night blindness                                                                                                                                                   | Effects usually are reversible after discontinuation of vincristine.<br>(Bobba & Klein, 2012; Kunkler et al., 2019; Singh & Singh, 2012)                                                                                                                                                                                                                                                                                         |
| <b>Hormone Therapy Agents</b>      |                                                                      |                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Aromatase inhibitors               | Anastrozole (Arimidex®), exemestane (Aromasin®), letrozole (Femara®) | Visual disturbances, retinal hemorrhages, hemiretinal artery occlusion, vitreoretinal traction, corneal epithelial cysts, dry eyes, impact on retinal and optic nerve function                                                                                          | (Chatziralli et al., 2016)                                                                                                                                                                                                                                                                                                                                                                                                       |
|                                    | Tamoxifen (Nolvadex®)                                                | Cataracts and decreased color vision; increased risk with doses > 20 mg daily; retinal toxicity (small refractile or crystalline dot-like yellowish deposits in the area surrounding the macula, in the nerve, and in plexiform layers); corneal opacities; retinopathy | A baseline ophthalmic examination is recommended within the first year. Visual acuity and macular edema may improve with tamoxifen withdrawal, but retinal deposits often do not.<br>Small doses (20–40 mg daily) can cause ocular side effects. The incidence rises with increasing total cumulative dose and duration of treatment.<br>(Bommireddy & Carrim, 2016; Gorin et al., 1998; Singh & Singh, 2012; Tsai et al., 2003) |
| <b>Immunotherapy Agents</b>        |                                                                      |                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Cytokines: interferons             | Interferon alpha, beta, and gamma                                    | Retinopathy, primarily retinal hemorrhages; cotton wool spots; disc edema<br>Vision changes, nonspecific conjunctivitis, and ocular pain are the most frequently reported ocular side effects.                                                                          | Risk is increased in patients with hypertension or diabetes and those receiving higher doses. Effects may occur as soon as 15 minutes after initial exposure or take many months to be apparent. Less than 1% of patients receiving interferon develop ocular toxicities.<br>(Bindiganavile et al., 2021; Kunkler et al., 2019; Willson, 2004)                                                                                   |
| Cytokines: interleukins            | Interleukin-2                                                        | Neuro-ophthalmic effects, including scotoma, diplopia, transient blindness, and visual hallucinations                                                                                                                                                                   | —                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Miscellaneous                      | Retinoids                                                            | Blepharoconjunctivitis, corneal opacities, papilledema, pseudotumor cerebri, night blindness                                                                                                                                                                            | Avoid concurrent use of tetracyclines and drugs causing intracranial hypertension.<br>(Al-Tweigeri et al., 1996; Fraunfelder et al., 2008)                                                                                                                                                                                                                                                                                       |

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**TABLE 25-3.** Ocular Toxicities of Antineoplastic Agents (*Continued*)

| Classification                                                                                                                                                   | Drug                                                                                                                   | Side Effects                                                                                                                                                                                        | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Immunotherapy Agents (Cont.)</b>                                                                                                                              |                                                                                                                        |                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Monoclonal anti-body: B-cell maturation antigen targeted                                                                                                         | Belantamab mafodotin (Blenrep®)                                                                                        | Dry eyes, blurry vision<br>Can cause keratopathy with marked microcyst-like deposits on corneal epithelium                                                                                          | Hold drug and refer to an ophthalmologist.<br>(Dolgin, 2020; Fortes et al., 2021)                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Monoclonal antibodies: check-point inhibitors (anti-cytotoxic T-lymphocyte antigen 4, anti-programmed cell death protein 1, anti-programmed cell death-ligand 1) | Ipilimumab (Yervoy®), nivolumab (Opdivo®), pembrolizumab (Keytruda®), atezolizumab (Tecentriq®), durvalumab (Imfinzi®) | Uveitis; iritis; papillitis; rare (< 1%) conjunctivitis, scleritis, episcleritis, blepharitis, and temporal arteritis; tearing; diplopia; orbital inflammation; keratitis; dry eyes; blurred vision | Uveitis, iritis, and papillitis were successfully treated with topical corticosteroid drops. Treatment consisted of discontinuing the agent and initiating adjunctive systemic or topical corticosteroids.<br>(Bhatti & Salama, 2018; Bitton et al., 2019; Cunningham et al., 2016; Emens et al., 2019; Fortes et al., 2021; Kunkler et al., 2019; Liu et al., 2020; Papavasileiou et al., 2016; Park et al., 2021; Puzanov et al., 2017; Shahzad et al., 2021; Young et al., 2021; Zimmer et al., 2016) |
| Monoclonal antibody: chimeric                                                                                                                                    | Rituximab (Rituxan®)                                                                                                   | Conjunctivitis, transient ocular edema, burning sensation, transient visual changes, or permanent and severe loss of visual acuity                                                                  | (Bhatti & Salama, 2018; Fortes et al., 2021; Singh & Singh, 2012)                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Monoclonal antibody–drug conjugate                                                                                                                               | Tisotumab vedotin (Tivdak®)                                                                                            | Visual disturbances secondary to the corneal epithelium and conjunctival changes, including vision loss and corneal ulceration                                                                      | An ophthalmic examination should be performed at baseline, prior to each dose, and as indicated.<br>Adhere to premedication and eye care before, during, and after infusions.<br>Withhold, reduce, or permanently discontinue depending on severity.<br>(Fortes et al., 2021; Seagen, 2021)                                                                                                                                                                                                              |
| Monoclonal antibodies: human                                                                                                                                     | Panitumumab (Vectibix®)                                                                                                | Keratitis and ulcerative keratitis, conjunctivitis, ocular hyperemia, increased lacrimation, eye or eyelid irritation, growth of eyelashes                                                          | The onset of ocular symptoms is 14–15 days after the first dose of panitumumab. Symptoms resolve after panitumumab is discontinued. The median time of resolution is 84 days.<br>(Amgen, 2017; Cunningham et al., 2016; Fortes et al., 2021; Liu & Kurzrock, 2015; Singh & Singh, 2012)                                                                                                                                                                                                                  |
| Monoclonal antibodies: humanized                                                                                                                                 | Bevacizumab (Avastin®)                                                                                                 | Lacrimation disorder, eye disorder, blurred vision; glaucoma                                                                                                                                        | The risk of glaucoma and having glaucoma surgery was greatly increased when patients received 7 or more injections.<br>(Bhatti & Salama, 2018; Eadie et al., 2017)                                                                                                                                                                                                                                                                                                                                       |

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**TABLE 25-3.** Ocular Toxicities of Antineoplastic Agents (*Continued*)

| Classification                                     | Drug                                                           | Side Effects                                                                                                                                                                                                                                                                   | Nursing Considerations                                                                                                                                                                                                                                                                               |
|----------------------------------------------------|----------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Immunotherapy Agents (Cont.)</b>                |                                                                |                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                      |
| Monoclonal anti-bodies: humanized ( <i>Cont.</i> ) | Pertuzumab (Perjeta®)                                          | Increased lacrimation                                                                                                                                                                                                                                                          | (Fortes et al., 2021)                                                                                                                                                                                                                                                                                |
|                                                    | Trastuzumab (Herceptin®), ado-trastuzumab emtansine (Kadcyla®) | Conjunctivitis, papilledema, retinal hemorrhage, dry eyes, increased lacrimation                                                                                                                                                                                               | (Bhatti & Salama, 2018; Fortes et al., 2021)                                                                                                                                                                                                                                                         |
| <b>Miscellaneous Agents</b>                        |                                                                |                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                      |
| Miscellaneous                                      | Bisphosphonates                                                | Conjunctivitis, uveitis, scleritis, episcleritis, eyelid edema, optic neuritis, periorbital edema, orbital inflammation                                                                                                                                                        | Bisphosphonates must be discontinued for symptoms to resolve.<br>Oral corticosteroids are used for severe inflammation or other symptoms.<br>Most reports describe the onset of symptoms within 48 hours of the initial infusion, flu-like symptoms, fever, or myalgia.<br>(Cunningham et al., 2016) |
|                                                    | Corticosteroids                                                | Posterior subcapsular cataracts, glaucoma, retinal hemorrhage, opportunistic eye infections, visual field defects, blurred vision, diplopia, exophthalmos, scleral discoloration<br>Increased intraocular pressure and subsequent glaucoma have been noted with long-term use. | (Loredo et al., 1972)                                                                                                                                                                                                                                                                                |
|                                                    | Cyclosporine A                                                 | Optic neuropathy, blurred vision, retinopathy, case reports of cortical blindness                                                                                                                                                                                              | A combination of cyclosporine A and total body irradiation may increase susceptibility to developing radiation-induced optic neuropathy; patients' symptoms improved to some extent when cyclosporine was discontinued.<br>(Mejico et al., 2000; Palmer et al., 2008)                                |
|                                                    | Deferoxamine mesylate/desferrioxamine (Deseferal®)             | Night blindness, visual field constriction, cataracts, pigmentary retinopathy, optic neuropathy; blurring vision, decreased visual acuity, vision loss, visual defects, scotoma, optic neuritis, corneal opacities, and impaired peripheral, color, and night vision           | Ocular side effects occur related to prolonged use and high doses or in patients with low ferritin levels<br>Ocular disturbances are reversible upon treatment discontinuation.<br>(Pfizer, 2021)                                                                                                    |

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**TABLE 25-3.** Ocular Toxicities of Antineoplastic Agents (*Continued*)

| Classification                                                            | Drug                     | Side Effects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Nursing Considerations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|---------------------------------------------------------------------------|--------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Miscellaneous Agents (Cont.)</b>                                       |                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Miscellaneous<br>(Cont.)                                                  | Ethambutol hydrochloride | Decreased visual acuity, color blindness, visual defect, possible irreversible blindness, optic neuritis                                                                                                                                                                                                                                                                                                                                                                                                                       | Ocular toxicity can happen at any dose but is increased at doses > 50 mg/kg; visual acuity changes can be unilateral or bilateral. Testing for visual acuity should be performed before treatment begins and periodically during treatment unless dose is > 15 mg/kg daily, in which monthly testing is needed. (STI Pharma, 2017)                                                                                                                                                                                                                                                                                                      |
|                                                                           | Mannitol (Osmitrol®)     | Blurred vision                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Because of fluid and electrolyte shifts, side effects can be prevented with close monitoring and test dose to evaluate the degree of renal failure when indicated. (Baxter Healthcare, 2011)                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                           | Tacrolimus (Prograf®)    | Optic neuropathy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | (Ascaso et al., 2012)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Targeted Therapy Agents</b>                                            |                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Monoclonal antibody: chimeric (epidermal growth factor receptor targeted) | Cetuximab (Erbix®)       | Blurred vision, eye pain, visual field cuts; blepharitis; eyelid dermatitis, conjunctivitis, poliosis (whitening of the eyelashes), corneal erosions, punctate keratitis<br>Relatively common: loss of eyelashes or eyebrows (madarosis) and cicatricial ectropion, loss of color of the skin around the eye with weekly infusions; trichomegaly<br>Very rare: bilateral ocular discomfort with itchiness around both eyelids, foreign body sensation, tearing associated with exfoliated skin, oil secretions, crusty scaling | Ocular side effects occurred in < 20% of patients and resolved after treatment was discontinued.<br>Blepharitis was treated with oxytetracycline cream 3 times daily for 20 days.<br>Madarosis and cicatricial ectropion resolved after discontinuation of cetuximab.<br>Ocular discomfort cleared with topical antibiotics and holding therapy. Many researchers recommend an ophthalmologist referral for patients experiencing trichomegaly if eye irritations occur, and eyelashes may be carefully and safely trimmed. (Fortes et al., 2021; Kunkler et al., 2019; Liu et al., 2020; Liu & Kurzrock, 2015; Moshirfar et al., 2021) |
| Small molecule inhibitors                                                 | Afatinib (Gilotrif®)     | Conjunctivitis, keratitis, blepharitis, corneal thinning and erosion, dry eyes, trichomegaly, uveitis                                                                                                                                                                                                                                                                                                                                                                                                                          | Ocular toxicity occurred in 13%–20% of patients; none were greater than grade 3. (Fortes et al., 2021; Fu et al., 2017; Kunkler et al., 2019; Shah & Shah, 2019)                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|                                                                           | Axitinib (Inlyta®)       | Retinal artery occlusion, retinal vein occlusion/thrombosis                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | (Fortes et al., 2021)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

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**TABLE 25-3.** Ocular Toxicities of Antineoplastic Agents (*Continued*)

| Classification                             | Drug                                                                                                                                                                                | Side Effects                                                                                                                                                                  | Nursing Considerations                                                                                                                                                                                                                        |
|--------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Targeted Therapy Agents (Cont.)</b>     |                                                                                                                                                                                     |                                                                                                                                                                               |                                                                                                                                                                                                                                               |
| Small molecule inhibitors ( <i>Cont.</i> ) | Binimetinib (Mektovi <sup>®</sup> ), Encorafenib (Braftovi <sup>®</sup> )                                                                                                           | Retinopathy                                                                                                                                                                   | Discontinuing the agent resolves retinopathy partially or completely. Retinal adverse events were resolved in most patients with agent discontinuation or dose reduction. (Fortes et al., 2021; van Dijk et al., 2016; Watanabe et al., 2016) |
|                                            | Bortezomib (Velcade <sup>®</sup> )                                                                                                                                                  | Chalazion                                                                                                                                                                     | Toxicity is reported as rashes, fatigue, and ocular inflammation. Effects start within 3 months of therapy. Discontinuing the agent has led to resolution or improvement. (Fortes et al., 2021; Fraunfelder & Yang, 2016)                     |
|                                            | Crizotinib (Xalkori <sup>®</sup> ), ceritinib (Zykadia <sup>®</sup> ), alectinib (Alecensa <sup>®</sup> ), brigatinib (Alunbrig <sup>®</sup> ), lorlatinib (Lorbrena <sup>®</sup> ) | Visual impairment, photopsia, blurred vision, vitreous floaters, photophobia, diplopia                                                                                        | Toxicities occurred in 62% of patients. Most events were grade 1 and started within 2 weeks. (Chelala et al., 2019; Davis, 2016; Fortes et al., 2021; Fu et al., 2017; Shah & Shah, 2019)                                                     |
|                                            | Dabrafenib (Tafinlar <sup>®</sup> )                                                                                                                                                 | Uveitis, iritis; central macular edema, photophobia                                                                                                                           | (Davis, 2016)                                                                                                                                                                                                                                 |
|                                            | Erdafitinib (Balversa <sup>™</sup> )                                                                                                                                                | Central serous retinopathy or retinal pigment epithelial detachment has been seen, with a reported $\geq$ grade 3 incidence.                                                  | The U.S. Food and Drug Administration requires a regular eye examination at least monthly for the first 4 months of treatment. (Fortes et al., 2021; Montazeri & Bellmont, 2020)                                                              |
|                                            | Erlotinib (Tarceva <sup>®</sup> )                                                                                                                                                   | Periorbital rash, conjunctivitis, eyelid ectropion, eyelash trichomegaly<br>Episcleritis and corneal abrasion related to infectious keratitis                                 | Side effects resolved within 6 weeks after treatment was discontinued. See cetuximab for comments regarding trichomegaly. (Davis, 2016; Fortes et al., 2021; Liu & Kurzrock, 2015; Singh & Singh, 2012)                                       |
|                                            | Gefitinib (Iressa <sup>®</sup> )                                                                                                                                                    | Common: conjunctivitis, blepharitis, dry eyes<br>Uncommon: corneal erosion related to eyelash growth (trichomegaly)<br>Very rare: corneal membrane sloughing, ocular ischemia | (Davis, 2016; Fortes et al., 2021; Liu & Kurzrock, 2015)                                                                                                                                                                                      |

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**TABLE 25-3.** Ocular Toxicities of Antineoplastic Agents (*Continued*)

| Classification                             | Drug                                      | Side Effects                                                                                                                                                                                                            | Nursing Considerations                                                                                                                                                                                                                                                                                                                    |
|--------------------------------------------|-------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Targeted Therapy Agents (Cont.)</b>     |                                           |                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                           |
| Small molecule inhibitors ( <i>Cont.</i> ) | Imatinib mesylate (Gleevec <sup>®</sup> ) | Periorbital edema; dry eyes; visual disorders such as blurred vision, reduced visual acuity, and visual disturbances; epiphora, optic neuritis, cystoid macular edema                                                   | Periorbital edema develops in 70% of patients and usually occurs 5–8 weeks after treatment starts. It can occur 24 hours after treatment starts or up to 1 year after, depending on dose. It is usually mild and does not require therapy. (Davis, 2016; Fortes et al., 2021; Fu et al., 2017; Liu & Kurzrock, 2015; Singh & Singh, 2012) |
|                                            | Nilotinib (Tasigna <sup>®</sup> )         | Hemorrhage, periorbital edema, pruritis, conjunctivitis, dry eyes<br>Rarely causes diplopia, photophobia, blepharitis                                                                                                   | Hold drug; refer to an ophthalmologist. (Bindiganavile et al., 2021)                                                                                                                                                                                                                                                                      |
|                                            | Pazopanib (Votrient <sup>®</sup> )        | Eyelash discoloration, eye edema                                                                                                                                                                                        | (Fortes et al., 2021)                                                                                                                                                                                                                                                                                                                     |
|                                            | Sunitinib (Sutent <sup>®</sup> )          | Periorbital edema; neurosensory retinal detachment; increased lacrimation; eyelid edema                                                                                                                                 | Effects resolve after epidermal growth factor receptor inhibitor treatment is discontinued. (Davis, 2016; Fortes et al., 2021)                                                                                                                                                                                                            |
|                                            | Trametinib (Mekinist <sup>®</sup> )       | Gradual or immediate loss of vision, including blind spots; temporarily or permanently blurred vision; dimness of vision; double vision; halo vision around lights; colorful spots or floaters; changes in color vision | Ocular toxic effects were seen in 15% of patients. (Bindiganavile et al., 2021; Davis, 2016; Fortes et al., 2021; Purbrick et al., 2017; Vishnevskia-Dai et al., 2021)                                                                                                                                                                    |
|                                            | Vandetanib (Caprelsa <sup>®</sup> )       | Conjunctivitis, corneal structure change, glaucoma, vortex keratopathies, cataract, dry eyes, blurred vision, visual impairment, halo vision, photopsia, accommodation disorders                                        | Cornea verticillata (brownish lines within the corneal epithelium) may develop. Complete regression of the cornea verticillata occurs after the drug is discontinued, but it may take several months to resolve. (Bindiganavile et al., 2021; Davis, 2016; Fortes et al., 2021)                                                           |
|                                            | Vemurafenib (Zelboraf <sup>®</sup> )      | Uveitis, iritis, retinal vein occlusion, blurry vision, photophobia, vision disorder                                                                                                                                    | Treatment may need to be held; refer to an ophthalmologist. (Fortes et al., 2021; Liu et al., 2020; Vishnevskia-Dai et al., 2021)                                                                                                                                                                                                         |

*Note.* This table may not include all antineoplastics that cause ocular toxicities. Review package inserts for dosing and prescribing information.

- (2) Inspect for color, vascular pattern, discharge, and any nodules or swelling.
- f) Cornea, lens, iris, and pupils
  - (1) Observe the cornea and lens for a smooth appearance, clarity, and any opacities in the lens.
  - (2) Test corneal reflex by gently touching a cotton swab to the corneal surface.
  - (3) Observe iris and pupils.
  - (4) Margins should be clearly identified.
  - (5) Observe the pupils for size, shape, and symmetry.
  - (6) If the pupils are larger than 5 mm or smaller than 3 mm, measure the pupils with a pupil guide (a card or penlight with black circles of varying sizes).
  - (7) Test the pupils for light reaction, observing for direct reaction (pupillary constriction in the same eye) and consensual reaction (pupillary constriction in the opposite eye).
  - (8) Note pain and photophobia.
- g) Extraocular muscles (cranial nerves)
  - (1) Observe for light reflex (shining a light in the patient's eyes and inspecting the reflections in the corneas) and extraocular movement by having the patient follow finger movements in six planes and convergence.
  - (2) Note any unilateral movement, lack of movement, nystagmus, lid lag, or other abnormal movements.

#### G. Collaborative management

1. Refer to an ophthalmologist for further evaluation and treatment (Dolgin, 2020; Fortes et al., 2021; Kunkler et al., 2019; Shah & Shah, 2019; Vishnevskia-Dai et al., 2021; Young et al., 2021).
2. Symptoms that necessitate a referral (Bhatti & Salama, 2018; Brahmer et al., 2018; Davis & Francis, 2017; Fu et al., 2017; Kunkler et al., 2019; Montazeri & Bellmunt, 2020; Munir & Aylward, 2017; National Cancer Institute Cancer Therapy Evaluation Program, 2017; Puzanov et al., 2017)
  - a) Persistent ocular pain, significant loss of vision, or decreased acuity of vision
  - b) Severe redness of the eye or light sensitivity
  - c) Trichomegaly
  - d) Failure to respond to treatment within one week of initiation for squamous blepharitis, meibomitis, or dysfunctional tear syndrome
3. Instruct patients to use pharmacologic management as appropriate (e.g., antibiotics, steroids, artificial tears).
4. To prevent further damage, discontinue the causative agent and promote symptom management.
5. Surgical interventions may be necessary (e.g., cataract surgery, dilation for punctal stenosis, enucleation).

#### H. Patient and family education

1. Teach patients self-examination techniques, emphasizing the importance of close monitoring and prompt reporting of any structural changes in eyelids or eyelashes or changes in vision.
2. Emphasize the importance of careful hygiene and handwashing techniques to minimize cross-contamination.
3. Demonstrate the proper use of eye drops and lubricants.
4. Encourage patients to schedule regular eye examinations (Brahmer et al., 2018; Davis & Francis, 2017; Durrechou et al., 2020; Fortes et al., 2021; Puzanov et al., 2017; Schoenfeld et al., 2020; Young et al., 2021).

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## SECTION VI

# Post-Treatment

Chapter 26. Post-Treatment and Survivorship Care



## CHAPTER 26

# Post-Treatment and Survivorship Care

### A. Overview

1. Fitzhugh Mullan coined the term *cancer survivorship*.
  - a) In 1985, he famously wrote about his experience with cancer and acknowledged that survivorship “begins at the point of diagnosis” (Mullan, 1985, p. 270).
  - b) Subsequently, major federal, public, and private cancer organizations have defined survivorship as beginning with diagnosis and continuing for the rest of life.
  - c) An important concept to understand is that survivorship includes people living with cancer.
2. Over the past 35 years, the number of cancer survivors in the United States has increased from 3 million to more than 16.9 million (American Cancer Society, 2019).
  - a) The number is expected to increase to 22.1 million (a 34% increase) by 2030 (American Cancer Society, 2019).
  - b) The past 20 years have seen a continuous decline in mortality in the most prevalent cancers—lung, breast, prostate, and colorectal (Siegel et al., 2022).
  - c) A decrease in tobacco use, earlier cancer diagnoses, and advances in cancer treatment have led to an improvement in five-year relative survival rates for all cancers from 49% in the 1970s to 66% for those diagnosed between 2014 and 2018 (Noone et al., 2018; U.S. Cancer Statistics, 2021).
  - d) In 2019, approximately 64% of survivors were aged 65 years or older (Miller et al., 2019).
  - e) The exponential growth in older survivors has been called the “silver tsunami.” An estimated 73% of cancer survivors will be aged 65 years or older by 2040 (Bluethmann et al., 2016).
  - f) In 2021, approximately 64% of survivors were diagnosed five or more years ago, 15% were diagnosed 20 or more years ago, and 5% were diagnosed 30 or more years ago (U.S. Cancer Statistics, 2021).
3. Childhood cancer survivors constitute 0.5%–3% of the cancer survivor population (Denlinger et al., 2014).
  - a) Approximately 85% of children and adolescents survive a cancer diagnosis (Siegel et al., 2022). However, long-term childhood cancer survivors are at risk for long-term effects from disease and treatment.
  - b) Research suggests that approximately 60%–90% of survivors of childhood cancers have one or more treatment- or disease-related long-term effect (Phillips et al., 2015).
  - c) The Children’s Oncology Group published long-term follow-up guidelines for screening and management of late effects for survivors of childhood cancer ([www.survivorshipguidelines.org](http://www.survivorshipguidelines.org)).
  - d) The organized research effort to prospectively follow childhood cancer survivors has provided data for long-term care recommendations. Data-driven recommendations for adults are often cancer type and treatment specific.
4. Adult cancer survivors
  - a) Currently, 64% of cancer survivors are aged 65 years or older, and almost half (47%) are aged 70 or older (Cancer.Net, 2019; Miller et al., 2019).
  - b) In the United States, the five-year relative survival rate is worse for Black people (62%) than for White or other races (66%), with Black women faring the worst (61.6%) (U.S. Cancer Statistics Working Group, 2021).
5. Long-term and late effects
  - a) In addition to the physical long-term and late effects of cancer and its treatment, cancer survivors may face psychological, financial, emotional, spiritual, and social challenges.
  - b) The number and types of continuing, long-term, and late effects experienced by survivors are influenced by the type and dose of treatments received.
6. Nursing
  - a) Nurses have multiple roles in the continuing care of cancer survivors.



- b) These roles include monitoring, assessing, and treating survivors for the effects of treatment that emerge after completion of therapy.
- c) Nurses have a vital role in teaching survivors about the advantages of a healthy lifestyle and other interventions to minimize the potential effects of cancer diagnosis and treatment.

## B. Cancer survivorship care

1. The goals of survivorship care were outlined in a seminal report by the Institute of Medicine (now the National Academy of Medicine) (Hewitt et al., 2006).
  - a) Surveillance for cancer spread, recurrence, and second cancers and assessment of medical and psychosocial late effects
  - b) Prevention of recurrent and new cancers and other late effects
  - c) Intervention for consequences of cancer and its treatment
  - d) Coordination between primary and specialty care
2. The essential elements of survivorship care to achieve these goals were defined by interprofessional clinical and research experts in 2011 (Livestrong, 2011). Accrediting organizations such as the American College of Surgeons Commission on Cancer (ACoS CoC, 2022) adapted these elements as services for optimal cancer care.
  - a) Services include screening for recurrence and new cancers, symptom management, health promotion education, care coordination, and a survivorship care plan (SCP), including a treatment summary (ACoS CoC, 2022).
  - b) Other recommended services include comprehensive medical and psychosocial assessment and care, a transition visit, nutrition services, rehabilitation, physical activity programs, psychiatric services, financial support, patient navigation, and family and caregiver support (ACoS CoC, 2022).
3. ACoS CoC (2022) requires accredited healthcare organizations to offer at least three survivorship care services and hire and support a cancer survivorship program coordinator. SCPs are recommended but no longer required.
4. Regular follow-up care for all cancer survivors is recommended.
  - a) The National Comprehensive Cancer Network (NCCN) provides evidence-based guidelines for disease-specific follow-up care.
  - b) Betty R. Ferrell developed a quality-of-life model for the physical, psychosocial, emotional, and spiritual well-being of cancer survivors. It can be used as a framework for the holistic assessment of cancer survivors (Ferrell & Hassey Dow, 1997).

- c) A holistic assessment can help target the type of survivorship care needed and facilitate person-centered care (Young et al., 2015).
- d) Early follow-up care should occur frequently and emphasize the management of continuing physical, psychological, financial, emotional, spiritual, and social effects of the disease, its treatment, and surveillance for and detection of disease recurrence.
- e) Long-term follow-up care focuses on anticipating and identifying late effects of the disease or treatment, assessing quality of life, and providing continued surveillance for disease recurrence.

## 5. Nursing

- a) Interprofessional cancer care teams, primary care providers, and other specialist providers often participate in post-treatment care, making coordination of care a crucial component of survivorship care (Salz & Baxi, 2016).
- b) Nurses often play the coordinator role.
- c) In addition, registered nurses and advanced practice nurses are identified as members of the cancer care team prepared to coordinate survivorship programs and deliver survivorship care, including SCPs, to survivors after treatment completion (ACoS CoC, 2022).
- d) Advanced practice nurses, known providers of cost-effective, quality patient care, deliver survivorship care following National Academy of Medicine goals (Thom et al., 2019).

## 6. Cancer SCPs

- a) Delivery and discussion of SCPs to all patients completing primary treatment are recommended by survivorship advocates and accrediting organizations (ACoS CoC, 2022). Despite the promise of SCPs, research trials have not yet demonstrated efficacy (Salz & Baxi, 2016).
- b) SCPs include general patient information, a treatment summary, a plan for cancer surveillance, recommendations for other cancer screening, suggested health behaviors, education about possible late effects specific to the cancer type, and treatment and support resources.
- c) Many organizations have developed templates for SCPs (American Society of Clinical Oncology, n.d.; Livestrong, n.d.; see Table 26-1).

## 7. Models of survivorship care

- a) Although different models for delivering survivorship care have been implemented, the superiority of one model has not yet been demonstrated, and models vary widely by institution.
- b) Models may include specialist-led, nurse-led, community-based, primary provider-led, or interprofessional or shared care (Powel & Seibert, 2017).

**TABLE 26-1.** Key Resources for Cancer Survivorship Information

| Organization and Website                                                                                                                                                                                                                                                                       | Description                                                                                                                                                   |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>American Cancer Society</b><br><a href="http://www.cancer.org/treatment/survivorship-during-and-after-treatment/survivorship-care-plans.html">www.cancer.org/treatment/survivorship-during-and-after-treatment/survivorship-care-plans.html</a>                                             | Information on diet and exercise for cancer prevention (see also Rock et al., 2020)<br>Information on survivorship care plans                                 |
| <b>American Society of Clinical Oncology Survivorship Compendium</b><br><a href="http://www.asco.org/news-initiatives/current-initiatives/cancer-care-initiatives/survivorship-compedium">www.asco.org/news-initiatives/current-initiatives/cancer-care-initiatives/survivorship-compedium</a> | E-Learning for healthcare professionals<br>Assessment and management of symptoms<br>Survivorship care plan templates                                          |
| <b>Cancer.Net</b><br><a href="http://www.cancer.net/survivorship/survivorship-resources">www.cancer.net/survivorship/survivorship-resources</a>                                                                                                                                                | Comprehensive cancer survivorship information, including general resources for cancer survivors of all ages and information for young adults, teens, and kids |
| <b>Centers for Disease Control and Prevention: Cancer Survivorship</b><br><a href="http://www.cdc.gov/cancer/survivors">www.cdc.gov/cancer/survivors</a>                                                                                                                                       | Comprehensive cancer survivorship information for survivors, caregivers, healthcare professionals, and researchers                                            |
| <b>National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology</b><br><a href="http://www.nccn.org/guidelines/category_1">www.nccn.org/guidelines/category_1</a>                                                                                                            | Clinical practice guidelines on many cancer-related topics, including survivorship, treatment by cancer type, specific populations, and supportive care       |
| <b>Oncology Nursing Society survivorship care plans</b><br><a href="https://voice.ons.org/topic/survivorship-care-plans">https://voice.ons.org/topic/survivorship-care-plans</a>                                                                                                               | Cancer-specific survivorship care plans and nursing considerations                                                                                            |

### C. Long-term and late effects of cancer treatment

1. Long-term effects occur during treatment and continue beyond the acute period of recovery from treatment. Late effects occur a significant time after the end of treatment.
2. Perhaps the most common long-term effect is fear of recurrence (Sharpe et al., 2018, Smith et al., 2020).
  - a) The fear can manifest in specific situations, such as waiting for cancer surveillance test results, or it may be a more global fear.
  - b) When the stress of living with uncertainty is global, it can contribute to a cluster of symptoms, such as sleep disturbance, fatigue, and cognitive changes (Guimond et al., 2020).
  - c) Financial toxicity, prolonged changes in social and professional roles, and disruption of life's meaning can contribute to the stress of living with uncertainty.
  - d) Guidelines on assessing and treating these symptoms can be found in the other chapters of this book and on the NCCN ([www.nccn.org](http://www.nccn.org)) and Oncology Nursing Society ([www.ons.org](http://www.ons.org)) websites.
3. The most serious and life-threatening late effects of cancer treatment are cardiovascular disease (CVD) and second primary cancers.
4. Nonmalignant late effects
  - a) Incidence
    - (1) Approximately 40%–70% of survivors will develop a health problem related to cancer or its treatment (Demoor-Goldschmidt &

de Vathaire, 2019). Age of diagnosis and treatment, comorbidities, and exposures increase the risk of developing a long-term or late effect from cancer treatment.

- (2) Female childhood cancer survivors are more likely than male survivors to have one or more chronic health condition (Oeffinger et al., 2006).
  - (3) The cumulative incidence of a chronic health condition in childhood cancer survivors is more than 70% within 30 years of the cancer diagnosis. More than 40% of these conditions will be severe, disabling, or fatal (Oeffinger et al., 2006). Hospitalization rates of childhood cancer survivors are 1.6 times the rate of the general U.S. population, indicating that while cure may be attainable for many children with cancer, the long-term health effects and costs associated with treatment-related long-term toxicities are notable (Kurt et al., 2012).
- b) Potential long-term and late effects (see Table 26-2)
- (1) Auditory
  - (2) Bladder
  - (3) Cardiovascular
    - (a) The most common long-term and late effects of the heart are cardiomyopathies, subclinical left ventricular dysfunction, coronary artery

**TABLE 26-2.** Potential Long-Term and Late Effects and Associated Treatments

| Function or System    | Associated Treatments                                                                                                                                                                                                                       | Potential Late Effects                                                                                                                                                        |
|-----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Auditory              | Platinum agents, head radiation therapy                                                                                                                                                                                                     | Hearing loss, tinnitus                                                                                                                                                        |
| Bladder               | Cyclophosphamide, pelvic and lumbar–sacral radiation, spinal surgery, cystectomy, prostatectomy                                                                                                                                             | Bladder fibrosis, incontinence, neurogenic bladder                                                                                                                            |
| Cardiovascular        | Anthracyclines, cyclophosphamide, cisplatin, 5-fluorouracil, taxanes, trastuzumab, radiation therapy                                                                                                                                        | Cardiomyopathy, ischemia, pericardial disease, arrhythmias, congestive heart failure, coronary artery disease, valvular heart disease                                         |
| Cognitive             | Intrathecal or high-dose methotrexate; high-dose cytarabine; adjuvant chemotherapy for breast cancer; systemic chemotherapy treatment for lung cancer, ovarian cancer, and lymphoma; cranial radiation; neurosurgery                        | Alterations in attention, concentration, memory, and mental processing speed; visual and auditory impairment; dementia                                                        |
| Endocrine             | Immunotherapy, corticosteroids, hormone therapy, head/neck and abdominal/pelvic radiation therapy, hematopoietic stem cell transplantation                                                                                                  | Hypothyroidism, hypopituitarism, hyperparathyroidism, adrenal dysfunction                                                                                                     |
| Gastrointestinal      | Head/neck, abdominal, and pelvic radiation therapy; head/neck, colorectal, and pelvic/spinal surgery; hematopoietic stem cell transplantation with chronic graft-versus-host disease                                                        | Diarrhea, constipation, incontinence, gastrointestinal tract strictures/fibrosis/vasculitis, obstruction, impaired swallowing, impaired absorption of nutrients, fistulas     |
| Hepatic               | Antimetabolites, abdominal radiation therapy, hematopoietic stem cell transplantation                                                                                                                                                       | Hepatitis B and C, hepatic dysfunction, cirrhosis, cholelithiasis                                                                                                             |
| Lymphatic             | Radiation therapy, melanoma excision, pelvic lymph node dissection, axillary lymph node dissection                                                                                                                                          | Lymphedema                                                                                                                                                                    |
| Multisystem           | Any treatment                                                                                                                                                                                                                               | Fatigue, sleep disturbance, chronic pain                                                                                                                                      |
| Neurologic—central    | High-dose intravenous and intrathecal methotrexate; high-dose cytarabine; head, brain, and neck radiation therapy; neurosurgery                                                                                                             | Motor and sensory deficits, leukoencephalopathy, stroke, seizures                                                                                                             |
| Neurologic—peripheral | Brachial or lumbosacral plexus radiation therapy, spinal surgery, vincristine, vinblastine, platinum agents, taxanes, bortezomib, thalidomide                                                                                               | Brachial plexopathy, peripheral neuropathy                                                                                                                                    |
| Ocular                | Corticosteroids, busulfan, tamoxifen, head and total body irradiation, neurosurgery, hematopoietic stem cell transplantation with graft-versus-host disease                                                                                 | Cataracts, glaucoma, retinopathy, ocular nerve palsy, xerophthalmia                                                                                                           |
| Oral                  | Head and total body irradiation, hematopoietic stem cell transplantation with graft-versus-host disease                                                                                                                                     | Xerostomia, tooth decay                                                                                                                                                       |
| Psychosocial          | Any cancer treatment                                                                                                                                                                                                                        | Fear of recurrence, adjustment disorder, depression, anxiety, post-traumatic stress disorder, altered body image, financial toxicity and health insurance coverage challenges |
| Renal                 | Cisplatin, methotrexate, nitrosoureas, nephrectomy, abdominal and total body irradiation                                                                                                                                                    | Renal dysfunction, hypertension, chronic kidney disease                                                                                                                       |
| Respiratory           | Alkylating agents, bleomycin, busulfan, and nitrosoureas; head/neck, chest, and total body irradiation/radiation therapy; head/neck surgery and pulmonary lobectomy; hematopoietic stem cell transplantation with graft-versus-host disease | Dyspnea, restrictive lung disease, pulmonary fibrosis, pneumonitis, idiopathic pneumonia syndrome, bronchiolitis obliterans                                                   |

(Continued on next page)

**TABLE 26-2.** Potential Long-Term and Late Effects and Associated Treatments

| Function or System  | Associated Treatments                                                                                                                                             | Potential Late Effects                                                                                                                     |
|---------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| Sexual/reproductive | Alkylating agents, abdominal/pelvic radiation and surgery, androgen-suppressing treatments                                                                        | Infertility; higher risk of miscarriage, preterm labor, and low birth-weight infants; erectile dysfunction; painful sex; diminished libido |
| Skeletal            | Alkylating agents, anthracyclines, taxanes, corticosteroids, hormone therapies, aromatase inhibitors, pelvic radiation therapy, orchiectomy, androgen deprivation | Osteopenia, osteoporosis, avascular necrosis                                                                                               |

Note. Based on information from Andersen et al., 2014; Bower et al., 2014; Given & Vachon, 2019; Hershman et al., 2014; Koelwyn et al., 2012; Lenihan & Cardinale, 2012; Marchese et al., 2011; National Comprehensive Cancer Network, 2021a, 2021b; Travis et al., 2012; Treanor & Donnelly, 2014; Valdivieso et al., 2012.

From "Late Effects of Cancer Treatment," by K.M. Slusser, in C.H. Yarbro, D. Wujcik, and B.H. Gobel (Eds.), *Cancer Nursing: Principles and Practice* (8th ed., p. 2031), 2018, Jones and Bartlett Learning. Copyright 2018 by Jones and Bartlett Learning. Adapted with permission.

disease, valvular heart disease, pericardial disease, and arrhythmias (see Chapter 16).

- (b) More than 50% of children treated for childhood cancers are at an increased risk for CVD 5–10 years following chemotherapy (Henning & Harbison, 2017).
- (c) Cardiotoxicity from commonly used anticancer drugs (e.g., anthracyclines, monoclonal antibodies, tyrosine inhibitors) may not occur or become clinically evident until 10–20 years after chemotherapy treatment (Henning & Harbison, 2017).
- (d) The risk of developing anthracycline-associated cardiotoxicity increases with the lifetime cumulative dose of doxorubicin at 400–550 mg/m<sup>2</sup>, with many survivors receiving lower doses (McGowan et al., 2017). All survivors treated with an anthracycline should be considered at risk for cardiac dysfunction.
- (e) Cisplatin can be detected in the blood 20 years after treatment (Fung et al., 2019). It is associated with an increased risk of obesity, dyslipidemia, and hypertension, contributing to CVD (Okwuosa et al., 2017).
- (f) Chest irradiation, particularly to the left side or mantle, increases the risk of coronary artery disease, congestive heart failure, peripheral vascular disease, and arrhythmias (NCCN, 2021b).
- (4) Endocrine: hypothyroidism, growth hormone deficiency, gonadal failure, panhy-

popituitarism, adrenal insufficiency or dysfunction, diabetes mellitus, hypopituitarism, hyperparathyroidism (Gebauer et al., 2019; Treanor & Donnelly, 2014)

- (5) Gastrointestinal: impaired swallowing; gastrointestinal tract strictures, fibrosis, or vasculitis; obstruction; impaired absorption of nutrients; fistulas; incontinence; diarrhea; constipation (Slusser, 2018)
- (6) Hepatic: liver dysfunction, cirrhosis, hepatitis B and C (Treanor & Donnelly, 2014)
- (7) Lymphatic: cancer-related lymphedema (National Cancer Institute, 2019)
- (8) Neurologic: cognitive impairment, leukoencephalopathy, visual and auditory impairment, brain atrophy, brain necrosis, dementia, brachial plexopathy, peripheral neuropathy (Treanor & Donnelly, 2014; see Chapter 24)
- (9) Ocular
  - (a) Cataracts occur most often after alkylating agents, tamoxifen, and glucocorticoid steroids (Bommireddy & Carrim, 2016; Prenskey et al., 2018).
  - (b) Ocular inflammation (e.g., uveitis, episcleritis) has been associated with checkpoint inhibitors and other immunotherapy agents (Kunkler et al., 2019; NCCN, 2021a; see Chapter 25).
- (10) Oral: xerostomia, dental caries, infection and gum disease, after radiation to head and neck, chemotherapy, chronic graft-versus-host disease (Barrett & Cassidy, 2019; Cancer.Net, 2020)
- (11) Pulmonary: pulmonary fibrosis, dyspnea, radiation pneumonitis, idiopathic pneumonia syndrome, bronchiolitis obliter-

ans, generally impaired pulmonary function (Treanor & Donnelly, 2014)

- (12) Psychosocial effects (McFarland & Holland, 2016)
    - (a) Psychosocial issues: social withdrawal, relationship issues, body image changes, sexuality issues
    - (b) Mental health disorders: adjustment, delirium, depression, anxiety, post-traumatic stress
    - (c) Financial and vocational issues: employment, access to health care, insurance, educational assistance
  - (13) Renal: nephropathy, chronic kidney disease (Treanor & Donnelly, 2014)
  - (14) Skeletal: osteopenia, osteoporosis, osteonecrosis (Treanor & Donnelly, 2014)
  - (15) Sexual and reproductive: gonadal failure; treatment-induced menopause; infertility; higher risk of miscarriage, preterm labor, and low birth-weight infants; sexual dysfunction, including loss of libido, erectile dysfunction, and pain (Treanor & Donnelly, 2014; see Chapter 20)
5. Malignant late effects
- a) A second primary cancer is a new cancer distinct from the original malignancy that does not represent metastatic disease from the first primary tumor (Wood et al., 2012).
  - b) Incidence of second cancers
    - (1) Approximately 15%–20% of cancers are second cancers (Demoor-Goldschmidt & de Vathaire, 2019; Donin, 2016).
    - (2) Cancer survivors have an increased risk of developing another malignancy, given the longer duration of cancer survivorship. The lifetime risk is as high as 33% in some populations and includes a greater risk for mortality. More than 8% of survivors diagnosed with one of the 10 most prevalent cancers were found to have a second cancer, the most common of which being lung cancer (Donin et al., 2016).
    - (3) The 30-year cumulative incidence of second cancers among survivors of childhood malignancies is 3.9% after chemotherapy, 9% after chemotherapy and radiation, and 10.8% after radiation when excluding nonmelanoma skin cancer (Turcotte et al., 2019).
  - c) Pathophysiology
    - (1) Chemotherapy and radiation therapy cause DNA damage, the mechanism that leads to apoptosis. However, if nonlethal DNA damage occurs, DNA repair is criti-

cal to prevent the development of a second cancer (Cowell & Austin, 2012).

- (2) Alkylating chemotherapy agents transfer an alkyl group to DNA, causing DNA mismatch and inhibition of DNA replication and transcription.
    - (a) A DNA mismatch repair mechanism is responsible for repairing this cell damage; otherwise, apoptosis occurs.
    - (b) If cells survive with a dysfunctional DNA mismatch repair or genomic instability, this may lead to malignancy (Allan & Travis, 2005; Cowell & Austin, 2012; Tward et al., 2007).
  - (3) Topoisomerase II inhibitors
    - (a) Topoisomerase II inhibitors cause double-stranded DNA breaks, which leads to apoptosis.
    - (b) If the cell survives, these DNA breaks may cause chromosomal translocations of the histone-lysine N-methyltransferase 2A (*KMT2A*) gene, formerly known as the myeloid lymphoid leukemia/mixed-lineage leukemia (*MLL*) gene, or other crucial transforming genes that can lead to leukemia (Allan & Travis, 2005; Cowell & Austin, 2012; Tward et al., 2007).
  - (4) Radiation therapy
    - (a) Radiation therapy deposits energy in or near DNA, resulting in genetic or epigenetic changes that cause apoptosis.
    - (b) If radiation induces variations in the DNA and the cells do not die, the variants are passed on to cellular progeny and may lead to malignant transformation (Gebauer et al., 2019; Travis et al., 2014).
  - (5) Chemotherapy and radiation therapy interact with other factors, such as tobacco exposure, genetic makeup, hormone status, and immune function, and contribute to the development of second cancers (Allan & Travis, 2005; Travis et al., 2014).
- d) Types of second primary cancers
- (1) The two major types of second cancers are acute myeloid neoplasms and solid neoplasms.
  - (2) The relative risk of treatment-related leukemia is generally most significant during the first five years after therapy (Wood et al., 2012).
  - (3) Solid tumors occur at least 5–10 years after treatment. The risk differs across

the age spectrum by type of malignancy, latency period, associated risk factors, and modifying influences (Ng et al., 2010).

- (4) Treatment-related acute myeloid leukemia/myelodysplastic syndrome generally presents within five years of chemotherapy and is most associated with alkylating agents or topoisomerase inhibitors.
- (5) Two types of treatment-related leukemia exist (Fung et al., 2019).
  - (a) Alkylating agent-induced acute myeloid leukemia (Fung et al., 2019)
    - i. Risk is associated with alkylating agents, such as cyclophosphamide, cisplatin, melphalan, chlorambucil, and nitrosoureas.
    - ii. The disease usually occurs five to eight years after treatment.
    - iii. Development is associated with myelodysplastic syndrome and deletion or loss of chromosome 5 or 7.
  - (b) Topoisomerase II inhibitor-induced acute leukemia (Fung et al., 2019)
    - i. Risk is associated with topoisomerase II inhibitors, such as etoposide, teniposide, mitoxantrone, and anthracyclines.
    - ii. The disease usually occurs two to three years after treatment.
    - iii. Occurrence is often not associated with preceding myelodysplastic syndrome.
    - iv. Development is associated with chromosomal translocations 11q23 or 21q22, and sometimes t(15;17).
- e) Treatment-related risk factors of second primary cancers
  - (1) Chemotherapy
    - (a) Chemotherapy is associated with a risk of second cancers, primarily treatment-related leukemia and, to a lesser extent, solid tumors (Cowell & Austin, 2012; Demoor-Goldschmidt & de Vathaire, 2019; Morton et al., 2019; Ng & Travis, 2008; Travis et al., 2010).
    - (b) Alkylating agents are associated with the greatest incidence of second cancers. Risk increases with higher cumulative doses (Turcotte et al., 2019).

(c) A higher cumulative dose increases the risk of treatment-related leukemia (Leone et al., 2011; Travis et al., 2010; Turcotte et al., 2019).

(d) Agents with known carcinogenic potential are noted in Chapter 6.

(2) Radiation therapy

(a) Radiation-induced second cancers tend to occur within or at the margins of the radiation field, and the risk increases with the dose of radiation and the extent of the radiation field (Demoor-Goldschmidt & de Vathaire, 2019; Wood et al., 2012).

(b) Radiation-induced second cancers can occur in the bone (e.g., sarcoma), breast, lung, cervical, prostate, skin, stomach, esophageal, thyroid, blood (e.g., myelodysplastic syndrome, leukemia), and lymph systems (e.g., Hodgkin lymphoma). They are often observed 5–10 years after treatment, and the risk persists for decades (Demoor-Goldschmidt & de Vathaire, 2019; Travis et al., 2014; Wood et al., 2012).

(c) Radiation-associated solid tumors are the most common second cancers (Ng et al., 2010).

(d) Cranial irradiation at 18–24 Gy (Gray) doses increases the risk for central nervous system malignancy by 17-fold after five years in acute lymphoblastic leukemia survivors (Erb & Vogel, 2013).

(e) The risk of a second cancer diagnosis was similar after intensity-modulated radiation versus three-dimensional conformal radiation therapy. In contrast, proton beam radiation therapy was associated with lower risk of a second cancer.

(f) The risk of second cancers is similar with involved-field radiation therapy compared to three-dimensional conformal radiation therapy. It is possibly lower in proton beam radiation therapy (Xiang et al., 2020).

(3) Combination chemotherapy and radiation

(a) Many cancers are treated with combination and, at times, concurrent therapy.

(b) Combination therapy increases the risk of late effects, including second cancers. Few high-quality stud-



- ies have reported the association of combination radiation and chemotherapy, including alkylating agents, with increased risk of second cancers (Morton et al., 2013; Oeffinger et al., 2006).
- (c) Exposure to one of five specific combinations is associated with a risk of having a severe health condition that is at least 10 times the expected risk of the general population (Oeffinger et al., 2006).
    - i. Chest irradiation plus bleomycin
    - ii. Chest irradiation plus an anthracycline
    - iii. Chest irradiation plus abdominal or pelvic irradiation
    - iv. An anthracycline plus an alkylating agent
    - v. Abdominal or pelvic irradiation plus an alkylating agent
  - (4) Immunotherapy
    - (a) Data on late effects of immunotherapy are emerging as agents are approved and individuals receive standard-of-care treatment with long-term follow-up.
    - (b) A unique attribute of immunotherapy treatment is the potential for long-term immunogenicity surveillance that can protect against future recurrence but may also have adverse sequelae for healthy cells.
    - (c) Most late effects (e.g., pneumonitis, pericarditis, enterocolitis) are reported in the context of case studies and are related to checkpoint inhibitors (Blevins Primeau, 2018).
    - (d) A cohort study reported a 43% rate of chronic immune-related adverse events from anti-programmed cell death protein 1 therapy in patients treated for melanoma. The most frequent events were mild and included endocrinopathies, arthritis, xerostomia, neurotoxicity, and ocular changes (Patrinely et al., 2021).
    - (e) Immunotherapy agents targeting the BRAF protein are used to treat melanoma and are being studied for use in other cancers. A meta-analysis showed a significantly higher risk of squamous cell carcinomas of the skin after receiving single-agent BRAF inhibitors for melanoma (Peng et al., 2017).
  - f) Survivor-related risk factors of second primary cancers
    - (1) Age
      - (a) Younger age at cancer diagnosis increases the risk of developing a second cancer (Friedman et al., 2010). The risk of developing subsequent cancer in childhood cancer survivors is increased three- to sixfold (Reulen et al., 2011).
      - (b) Developing organs in younger patients may be especially vulnerable to the effects of medication and radiation (Ng et al., 2010).
      - (c) Older patients who experience adverse effects from a disease or its treatment may be unable to compensate for lost function, leading to less physical activity.
    - (2) Sex: Overall, women have a slightly higher risk of second cancers than men (Friedman et al., 2010; Miller et al., 2019; Turcotte et al., 2019).
    - (3) Genetic predisposition
      - (a) Survivors with genetic phenotypes that contributed to the development of their original cancer are at increased risk for second cancers.
      - (b) Common syndromes identified with increased risk are hereditary breast and ovarian cancer and hereditary nonpolyposis colorectal cancer (Lynch syndrome) (Wood et al., 2012).
      - (c) Immunodeficiency increases the risk of second cancers. Immune dysregulation may be associated with primary cancers, such as leukemia and lymphoma, or with immunosuppressive treatment (Brewer et al., 2014; Inamoto et al., 2015; Ng, 2014; Visentin et al., 2017).
      - (d) Infections such as human papillomavirus may increase the risk of second cancers in survivors of cervical and head and neck cancers. Human papillomavirus and hepatitis B and C increase the risk in hematopoietic stem cell transplantation (HSCT) recipients (Diaz et al., 2016; Inamoto et al., 2015; Ng & Travis, 2008).
    - (4) Exposures

- (a) Tobacco and alcohol exposure increase the risk of developing a second cancer in all cancer survivors (Wood et al., 2012). Approximately 4% of newly diagnosed cancer cases in 2020 were associated with alcohol consumption (Rumgay et al., 2021).
  - (b) Sun overexposure and tanning bed exposure increase the risk of developing skin cancer (U.S. Food and Drug Administration, 2015). Cancer survivors who have received chemotherapy, immunotherapy, and radiation are more likely to develop skin cancer (Huang et al., 2019; Teeppen et al., 2019).
- (5) Diet and exercise: Caloric excess, a diet low in fruits and vegetables, obesity, and physical inactivity increase the risk of second cancers involving the upper aerodigestive tract, colon, breast, and female reproductive organs (Rock et al., 2020; Wood et al., 2012).
- g) Risk of late effects for patients with select primary cancers and survivor populations: Select cancers are highlighted based on available long-term data.
- (1) Breast cancer
    - (a) Breast cancer survivors are at risk for cardiotoxicity from anthracyclines or trastuzumab, chemotherapy-induced premature menopause, osteoporosis, chemotherapy-induced cognitive impairment, sexual dysfunction, and taxane-related neuropathy (Azim et al., 2011; Ganz & Hahn, 2008).
    - (b) Breast cancer survivors younger than age 40 years at the time of diagnosis and carriers of a genetic predisposition (e.g., *BRCA2*, *TP53*) are at increased risk for second cancers (Azim et al., 2011; Erb & Vogel, 2013). This increased risk may also be attributed to treatment modality and reproductive, environmental, or other genetic factors (Molina-Montes et al., 2015).
      - i. Chemotherapy
        - The incidence of myelodysplastic syndrome and acute myeloid leukemia is higher in breast cancer survivors who have received alkylating agents, antimetabolites, platinum-based agents, and topoisomerase inhibitors. A longer duration of exposure to these agents increases the risk (Shenolikar et al., 2018).
      - Cumulative incidence is 0.5% at 8–10 years after anthracycline and cyclophosphamide chemotherapy (Erb & Vogel, 2013).
      - Other possible cancers include sarcoma, melanoma, and cancers of the salivary gland, esophagus, stomach, colon, breast, uterine corpus, ovary, and thyroid (Curtis et al., 2006; VanderWalde & Hurria, 2011).
    - ii. Hormone therapy: Risk of endometrial cancer after tamoxifen is 35% (Erb & Vogel, 2013).
    - iii. Radiation therapy
      - Radiation to the breast increases the risk of lung cancer, esophageal cancer, and sarcoma in all survivors. It also increases the risk of contralateral breast cancer in patients aged younger than 45 years (Azim et al., 2011; Ng et al., 2010; Travis et al., 2014).
      - The risk for sarcoma is SIR (standard incidence ratio) 3–6, with a latency period of 5–10 years (Erb & Vogel, 2013).
- (2) Cervical cancer
  - (a) Cervical cancer survivors have an increased risk for human papillomavirus-related (i.e., pharynx, genital sites, and rectum/anus) and smoking-related cancers (i.e., pharynx, trachea, bronchus, lung, pancreas, and urinary bladder) (Chaturvedi et al., 2007).
  - (b) An increased risk for second cancers exists for 40 or more years in women who have received pelvic irradiation to the colon, rectum/anus, urinary bladder, ovary, or genitals (Curtis et al., 2006; Travis et al., 2014).
  - (c) The 40-year cumulative risk of any second cancer is 22% among women diagnosed with cervical can-

cer before age 50 years and 16% for those diagnosed after age 50 years (Chaturvedi et al., 2007).

(3) Hodgkin lymphoma

(a) The leading causes of death in Hodgkin lymphoma survivors are second cancers and CVD (Matasar et al., 2015; Ng & van Leeuwen, 2016).

(b) Survivors treated with radiation therapy are at greater risk for second cancers and CVD than those treated with chemotherapy alone (Ng et al., 2011).

(c) Second primary cancers: Hodgkin lymphoma survivors are at risk for leukemia and solid tumors, particularly lung and breast cancer (Ng & van Leeuwen, 2016).

i. Solid tumors account for 75%–80% of all second cancers following treatment for Hodgkin lymphoma, and the risk is significantly increased with radiation (Ng et al., 2010).

ii. Radiation therapy, compared to chemotherapy for Hodgkin lymphoma, was associated with a higher risk for second and third malignancies during the first five years of follow-up (van Eggermond et al., 2014).

- The cumulative incidence of any second cancer following radiation is 11% for males and 26% for females, with the difference due to breast cancer. Other common solid tumors include thyroid and bone (Travis et al., 2014).

- The cumulative risk of second cancers following treatment with 40–45 Gy of extended-field or mantle radiation therapy is approximately 30% at 30 years (Hodgson, 2011).

- Modern radiation therapy for Hodgkin lymphoma uses involved-field radiation therapy, which treats only the lymph node regions initially involved. Prescribed radiation doses are 20–30 Gy. This reduces the volume of healthy

tissue exposed to radiation and significantly decreases the risk of second cancers (Hodgson, 2011; Koh et al., 2007).

iii. Breast cancer (Oeffinger et al., 2013)

- The risk of breast cancer in Hodgkin lymphoma survivors is significantly increased, particularly for women treated with chest irradiation before age 30 years.

- The latency period is 8–10 years following treatment.

- The risk of breast cancer appears to decrease in patients who reduce lifetime exposure to endogenous estrogens, such as those who experience ovarian failure or premature menopause.

iv. Lung cancer: The risk of lung cancer is associated with radiation therapy, alkylating agents, and smoking (Oeffinger et al., 2013).

(d) CVD: Hodgkin lymphoma survivors have a three- to fivefold increased risk of CVD, which generally manifests 10 years after therapy and persists for more than 25 years (Ng et al., 2011).

i. Coronary artery disease is the most common cardiovascular toxicity among Hodgkin lymphoma survivors and accounts for approximately 40%–50% of adverse cardiac events (Hodgson, 2011).

ii. Valvular disease is less common. It typically has a late onset (more than 10 years after radiation therapy) and is related to higher doses (greater than 30 Gy) or young age at treatment (Hodgson, 2011).

iii. Acute pericarditis is uncommon but may occur following radiation therapy with a large cardiac volume (Hodgson, 2011).

iv. Hodgkin lymphoma survivors treated with mantle radiation therapy at doses of 35–45 Gy are estimated to have a two- to

- fourfold increased risk of cardiac morbidity.
- v. The cumulative risk of significant heart disease among survivors of adult Hodgkin lymphoma is approximately 5%–10% at 15 years, 16% at 20 years, and 34% at 30 years (Hodgson, 2011).
  - (e) Hodgkin lymphoma survivors have an increased risk of treatment-related pulmonary toxicity, including radiation pneumonitis and bleomycin toxicity (Ng et al., 2011).
- (4) Lung cancer: Possible second cancers from alkylating agents are leukemia with SIR of 1.47 for non-small cell lung cancer and 6.57 for small cell lung cancer (Erb & Vogel, 2013).
- (5) Non-Hodgkin lymphoma
- (a) The relative risk of second cancers in non-Hodgkin lymphoma survivors is 1.8 times greater than the risk of the general population (Pirani et al., 2011).
  - (b) Survivors are at increased risk for acute myeloid leukemia, sarcomas, melanoma, Hodgkin lymphoma, and cancers of the bladder, head and neck, lung, gastrointestinal system, kidney, and thyroid (Tward et al., 2007).
    - i. Chemotherapy increases the risk of acute myeloid leukemia, lung cancer, and bladder cancer.
    - ii. Radiation therapy increases the risk of sarcomas, breast cancer, and mesothelioma.
- (6) Prostate cancer
- (a) Androgen deprivation therapy causes intended hypogonadism and possible osteoporosis (Shapiro et al., 2019).
  - (b) Possible second cancers from chemotherapy are melanoma, small intestine, soft tissue, bladder, thyroid, and thymus cancer (American Cancer Society, 2020; Curtis et al., 2006; Ng et al., 2010).
  - (c) After radiation to the pelvis, there is an increased risk of bladder cancer, colorectal cancer, and leukemia. The rate of second cancers from radiation for prostate cancer was 0.1%–3.8% for bladder cancer, 0.3%–4.2% for colon cancer, and 0.3%–1.2% for rectal cancer (Wallis et al., 2016). The colorectal cancer risk is similar to having a first-degree relative with colorectal cancer.
- (7) Testicular cancer
- (a) Testicular cancer is highly curable for men aged 18–39 years, with 95% living for 10 years or longer (Fung et al., 2019).
  - (b) The most common and concerning late effect for testicular cancer survivors is infertility. Regardless of planned therapy, sperm banking should be offered.
  - (c) Hypogonadism can occur, especially after chemotherapy, commonly cisplatin, etoposide, and bleomycin. Hypogonadism decreases sexual function, energy, muscle strength, and mood and is associated with metabolic syndrome (Fung et al., 2019).
  - (d) An increased risk of cardiotoxicity exists, including myocardial infarction, coronary artery disease, hyperlipidemia, and metabolic syndrome (Ng et al., 2011; Travis et al., 2010).
  - (e) Late pulmonary inflammation and fibrosis from bleomycin are rare and more likely to occur with a history of lung surgery, a greater than or equal to 20 pack-year history of tobacco smoking, and a cumulative cisplatin dose of more than 850 mg. One study suggests the *HFE* gene may affect the rate of bleomycin-induced pulmonary toxicity (Fung et al., 2019).
  - (f) Nephrotoxicity can occur in decreased glomerular filtration rate from cisplatin (Fung et al., 2019; Travis et al., 2010).
  - (g) Raynaud phenomenon is vascular damage caused by bleomycin. Symptoms occur in 18%–39% of survivors 4–12 months after bleomycin administration (Fung et al., 2019).
  - (h) A significant risk of leukemia and solid tumors exists. The risk of second cancers increases with younger age at treatment. The median time to occurrence is 20 years (van den Belt-Dusebout et al., 2007).
    - i. Chemotherapy increases the risk of radiation-associated

- second cancers (van den Belt-Dusebout et al., 2007).
  - ii. Risk of cisplatin- or etoposide-induced leukemia (0.5%–2%) is dose dependent (Fung et al., 2019; Travis et al., 2010).
  - iii. Risk of cisplatin-induced solid cancers shows a 1.4-to-2.4-fold increase (Fung et al., 2019). The most frequent types of solid cancers are thyroid, kidney, and gastrointestinal (Fung et al., 2019).
  - iv. Among 10-year testicular cancer survivors, a statistically significant increased risk exists of malignant melanoma and cancers of the lung (relative risk [RR] = 1.5, 95% confidence interval [CI] [1.2, 1.7]); thyroid, esophagus, pleura, and stomach (RR = 4, 95% CI [3.2, 4.8]); and pancreas, colon, rectum, kidney, bladder, and connective tissue (RR = 4, 95% CI [2.3, 6.3]) (Travis et al., 2005, 2012).
  - v. Radiation to the abdomen and pelvis increases leukemia risk threefold, with a mean latency of five years. Infradiaphragmatic radiation therapy fields were higher (RR = 2.7) than unexposed sites and remained elevated for 35 years (Fung et al., 2019).
  - vi. Gastric radiation doses greater than or equal to 50 Gy cause a 5.9-fold risk of gastric cancer (Fung et al., 2019).
- (8) Pediatric malignancies
  - (a) The risk of second cancers among childhood cancer survivors is associated with radiation therapy, chemotherapy, and genetic predisposition (Henderson et al., 2012; Travis et al., 2014). The risk of second cancers varies based on survivor age at exposure and the years since treatment (Hawkins et al., 2020).
  - (b) Second cancers often occur 10 or more years after treatment. Specific groups of pediatric cancer survivors have a 10-fold increase in developing second cancers based on treatment received, behaviors such as smoking tobacco and drinking alcohol, and the presence of rare genetic variants (Hawkins et al., 2020).
  - (c) The 30-year cumulative incidence of all second cancers in survivors of childhood cancer from 1970 to 1986 was 20.5% (95% CI [19.1, 21.8]) and was higher for patients who had received radiation therapy than for those who had not (25% vs. 10%) (Friedman et al., 2010; National Cancer Institute, 2022; Travis et al., 2014).
    - i. Second cancers with a 30-year cumulative incidence were nonmelanoma skin cancer (9.1%), other malignancies (7.9%), and meningioma (3.1%), with higher incidence for survivors who received radiation than those who did not (10% vs. 5%) (Friedman et al., 2010; Hawkins et al., 2020; National Cancer Institute, 2022; Travis et al., 2014).
    - ii. Among survivors of childhood cancer treated in the 1990s, the risk of second cancers at 15 years from cancer diagnosis was lower than those treated in the 1970s due to decreased use of radiation (Turcotte et al., 2017).
  - (d) Chemotherapy increases the risk of hematologic and solid second cancers, depending on chemotherapy type and cumulative dose (Hawkins et al., 2020).
    - i. Pediatric survivors exposed to chemotherapy only have a 2.8-fold increase in risk of second cancers compared to the general population.
    - ii. Exposure to alkylating agents increases the risk for gastrointestinal, thyroid, lung, breast, and bladder cancers; melanomas; and sarcomas. Cyclophosphamide increases sarcoma risk in a dose-dependent manner. Equivalent doses greater than 18,000 mg/m<sup>2</sup> increase breast cancer risk threefold (SIR: 3; 95% CI [1.2, 7.7]). Pro-

carbazine and cisplatin have been associated with 3.2-fold (95% CI [1.1, 9.4]) and 7.6-fold (95% CI [2.3, 25.5]) increased risk of gastrointestinal second cancers.

- iii. The risk for breast cancer treated with more than 250 mg/m<sup>2</sup> of anthracycline and no chest radiation was increased by nearly fourfold compared to the general population (SIR: 3.8; 95% CI [1.7, 8.3]).

(9) HSCT recipients are at risk for post-transplant lymphoproliferative disorders, treatment-related acute leukemia/myelodysplastic syndrome, and second solid tumors.

(a) In autologous HSCT recipients for lymphoma, the cumulative incidence of second acute leukemia/myelodysplastic syndrome was 3.09% at five years and 4.52% at 10 years (Tarella et al., 2011).

- i. The cumulative incidence of solid tumors was 2.54% at five years and 6.79% at 10 years.
- ii. The risk of solid tumors was associated with advanced age and radiation therapy.

(b) Allogeneic HSCT recipients were twice as likely to develop a solid tumor when compared to the general population.

- i. Risk was related to age younger than 30 years at transplantation and exposure to radiation therapy (Bhatia, 2014).
- ii. Allogeneic HSCT recipients with chronic graft-versus-host disease have a greater chance of developing skin and oral cancers (Gündüz et al., 2017; Rambhia et al., 2018).

(c) The risk of a post-transplant malignancy increases with younger age at the time of transplant, especially for those younger than 17 years (Serrano et al., 2017).

- i. Approximately 7% of pediatric HSCT recipients develop a second cancer by 20 years after transplant.
- ii. Lymphoproliferative disorders usually occur within two years.

iii. Therapy-related acute myeloid leukemia/myelodysplastic syndrome usually occurs three to seven years after transplant.

iv. Treatment-related leukemia mainly occurs in autologous recipients and is related to previous chemotherapy with alkylating agents or topoisomerase II inhibitors.

v. A wide range of solid second cancers have been described as occurring 10 or more years after HSCT and are primarily treatment related (Bomken & Skinner, 2015).

(d) Relative risk of thyroid carcinoma in HSCT recipients is 3.26 overall, with a significantly increased risk associated with age younger than 10 years, radiation therapy, female sex, and chronic graft-versus-host disease (Cohen et al., 2007).

## 6. Screening and early detection of late effects

### a) Cancer (NCCN, 2021b)

- (1) Survivors should follow adult cancer screening recommendations. This is especially important for childhood cancer survivors who have an additional risk for premature development of adult cancers (Children's Oncology Group, 2018; NCCN, 2021b).
- (2) Irradiated skin and soft tissues should be thoroughly and regularly evaluated for skin cancer throughout the life of survivors who have received chemotherapy, immunotherapy, or radiation therapy and undergo regular skin assessment.
- (3) Women younger than 30 years old who received greater than or equal to 10 Gy radiation to the chest should have a mammogram and magnetic resonance imaging at age 30 or eight years after exposure to radiation, whichever comes last (NCCN, 2021a). They should perform breast self-examination monthly beginning at puberty, and a clinical breast examination should be performed annually.

### b) Noncancer

- (1) Regular dental cleaning should be performed.
- (2) Routine vision examination should be performed.
- (3) Bone mineral density tests are indicated for survivors who are advanced in age,



- have limited or no gonadal function (e.g., hypogonadism, menopause), take chronic glucocorticosteroids, smoke tobacco, drink excessive alcohol, are frail, have an increased risk of falls, have an adult history of nontraumatic fractures, or a parental history of hip fracture (Shapiro et al., 2019).
7. Preventive health (NCCN, 2021b)
    - a) Healthcare providers have the opportunity to counsel cancer survivors about behaviors that promote health, including nutrition, exercise, avoidance of tobacco, and limited consumption of alcohol.
    - b) Health promotion behaviors decrease the risk for some second cancers and reduce comorbidity (Travis et al., 2013).
    - c) Regular physical exercise and a healthy diet appear to lower the risk of cancer recurrence and increase overall survival in multiple cancer survivor groups, including breast, colorectal, prostate, and ovarian cancer (Rutledge & Demark-Wahnefried, 2016).
      - (1) Eating a diet high in fruits, vegetables, and whole grains and low in red and processed meats protects against cancer progression, risk of recurrence, and overall mortality for various cancers. Nutritional counseling from a registered dietitian can be beneficial.
      - (2) Regular physical exercise appears to be associated with a lower risk for recurrence and improved survival following treatment for breast, prostate, ovarian, and colorectal cancers.
      - (3) Regular exercise also minimizes the long-term symptoms associated with cancer treatment.
      - (4) Physical activity programs and rehabilitation can assist survivors in establishing exercise habits, gaining strength, and adapting to physical limitations from treatment.
    - d) Cancer survivors who are overweight or obese may benefit from intentional weight loss following treatment. Cancer survivors who are underweight may benefit from appropriate weight gain.
    - e) Cancer survivors should obtain nutrients from foods instead of supplements or vitamins.
    - f) Cancer survivors should be offered routine vaccinations and encouraged to visit with a primary care provider regularly.
  8. Patient and family education
    - a) Provide information about the treatment and potential late effects of the disease and its treatment.
    - b) Explain the risks of second cancers, the typical time to onset, cancer screening recommendations, and the importance of follow-up visits.
    - c) Promote healthy lifestyle practices (NCCN, 2021b).
      - (1) Nutrition (Rock et al., 2020)
        - (a) A diet high in fruits, vegetables, and whole grains is associated with a lower risk of death than one that contains a high intake of processed and red meats, refined grains, sugar, and high-fat dairy products.
        - (b) It is recommended to ingest 1,000–1,200 mg of calcium and 800–1,000 IU of vitamin D daily (Shapiro et al., 2019).
        - (c) Avoid vitamin supplements and obtain nutrients from food.
      - (2) Regular physical exercise
      - (3) Tobacco avoidance and smoking cessation
      - (4) Alcohol limitation
      - (5) Sun protection practices
      - (6) Stress modification
      - (7) Sleep quality
      - (8) Offer relevant educational and support resources.
  9. Professional education
    - a) Continue learning about cancer survivorship care and possible long-term and late effects of established and emerging treatments.
    - b) Contribute to the interprofessional discussion about methods to effectively deliver survivorship care.
    - c) Consider using an SCP to communicate potential long-term and late effects of treatment and recommend follow-up to patients, caregivers, and primary care providers who may be unfamiliar with cancer and its treatments. A discussion of the SCP with primary care providers may be required (Iyer et al., 2017).

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# Appendices

- Appendix A. Clinical Practicum Evaluation: Part I
- Appendix B. Clinical Practicum Evaluation: Part II
- Appendix C. Sample Chemotherapy Order Template
- Appendix D. Antineoplastic Treatment Safety Checklist
- Appendix E. Consent for Antineoplastic Drug Treatment
- Appendix F. Distress Thermometer
- Appendix G. Hazardous Drug Administration Safe Handling Checklist
- Appendix H. Extravasation
- Appendix I. Vesicant Drug Extravasation Record



**APPENDIX A. Clinical Practicum Evaluation: Part I**

| ANTINEOPLASTIC THERAPY ADMINISTRATION COMPETENCY                                                                                                                                                                                                                                                                                                                                                                                                                                   |      |                    |  |  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|--------------------|--|--|
| Employee Name _____                                                                                                                                                                                                                                                                                                                                                                                                                                                                |      |                    |  |  |
| The RN evaluator who verifies competence in antineoplastic therapy administration must observe practice and validate that the nurse meets all of the following criteria.                                                                                                                                                                                                                                                                                                           |      |                    |  |  |
| RN Evaluators                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Date | Drugs Administered |  |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |      |                    |  |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |      |                    |  |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |      |                    |  |  |
| PRIOR TO ADMINISTRATION                                                                                                                                                                                                                                                                                                                                                                                                                                                            |      | Initials           |  |  |
| Reviews treatment plan with the RN evaluator, verifying regimen, protocol, treatment cycle, and day of cycle                                                                                                                                                                                                                                                                                                                                                                       |      |                    |  |  |
| Coordinates time of administration with pharmacy and others, as needed                                                                                                                                                                                                                                                                                                                                                                                                             |      |                    |  |  |
| Verifies documentation of consent for treatment (if applicable)                                                                                                                                                                                                                                                                                                                                                                                                                    |      |                    |  |  |
| Verifies that criteria to treat (e.g., laboratory data) are within acceptable parameters and reports results to provider as needed                                                                                                                                                                                                                                                                                                                                                 |      |                    |  |  |
| Completes physical assessment to ensure that no existing toxicities would preclude administration of the antineoplastic therapy (e.g., peripheral neuropathy, immuno-oncology toxicities)                                                                                                                                                                                                                                                                                          |      |                    |  |  |
| Completes review of response to previous therapy                                                                                                                                                                                                                                                                                                                                                                                                                                   |      |                    |  |  |
| Performs independent double check of original orders with a second RN for accuracy of the following <ul style="list-style-type: none"> <li>• Date of treatment</li> <li>• Agents</li> <li>• Dose calculation methodology (e.g., body surface area, area under the curve, mg/kg)</li> <li>• Drug dose</li> <li>• Schedule/sequence</li> <li>• Route</li> </ul>                                                                                                                      |      |                    |  |  |
| Verifies patient understanding of treatment goals, administration procedures, potential side effects, and when and how to contact the healthcare team                                                                                                                                                                                                                                                                                                                              |      |                    |  |  |
| Verifies that premedication, prehydration, and other preparations are completed and documented                                                                                                                                                                                                                                                                                                                                                                                     |      |                    |  |  |
| Verifies drug appearance and expiration date and/or time                                                                                                                                                                                                                                                                                                                                                                                                                           |      |                    |  |  |
| ADMINISTRATION                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |      |                    |  |  |
| Applies personal protective equipment, closed-system drug-transfer device (when the dosage form allows), and uses safe handling precautions                                                                                                                                                                                                                                                                                                                                        |      |                    |  |  |
| Applies filter and/or special tubing, if required by manufacturer                                                                                                                                                                                                                                                                                                                                                                                                                  |      |                    |  |  |
| Compares original order to dispensed drug label at the bedside or chairside with a second RN                                                                                                                                                                                                                                                                                                                                                                                       |      |                    |  |  |
| Verifies two patient identifiers (cannot use a room or chair number)                                                                                                                                                                                                                                                                                                                                                                                                               |      |                    |  |  |
| Verifies the presence of vascular access appropriate to the treatment plan (location, type)                                                                                                                                                                                                                                                                                                                                                                                        |      |                    |  |  |
| Assesses patency of vascular access device and ensures blood return is present                                                                                                                                                                                                                                                                                                                                                                                                     |      |                    |  |  |
| Demonstrates safe administration: <ul style="list-style-type: none"> <li>• <b>For IV push or IV minibag of vesicant medications:</b> Administers through side arm hub closest to patient, through a free-flowing IV; checks patency every 2–5 ml (every 2–3 ml for pediatric patients)</li> <li>• <b>For infusions:</b> Verifies appropriate rate of administration and infusion pump settings with a second RN; verifies blood return/patency per institutional policy</li> </ul> |      |                    |  |  |
| Demonstrates appropriate monitoring/observation for specific acute drug effects                                                                                                                                                                                                                                                                                                                                                                                                    |      |                    |  |  |
| Verbalizes appropriate action in the event of infiltration or extravasation                                                                                                                                                                                                                                                                                                                                                                                                        |      |                    |  |  |
| Verbalizes appropriate action in the event of hypersensitivity or anaphylactic reaction                                                                                                                                                                                                                                                                                                                                                                                            |      |                    |  |  |
| Verbalizes appropriate action in the event of a hazardous drug spill                                                                                                                                                                                                                                                                                                                                                                                                               |      |                    |  |  |
| AFTER ADMINISTRATION                                                                                                                                                                                                                                                                                                                                                                                                                                                               |      |                    |  |  |
| Flushes line with compatible fluid to clear IV tubing of drug                                                                                                                                                                                                                                                                                                                                                                                                                      |      |                    |  |  |
| Removes peripheral IV device or flushes/maintains central venous access device, as appropriate to patient needs                                                                                                                                                                                                                                                                                                                                                                    |      |                    |  |  |
| Doffs personal protective equipment and disposes of hazardous drug waste according to policy                                                                                                                                                                                                                                                                                                                                                                                       |      |                    |  |  |
| Documents medications, dose verification, and patient response                                                                                                                                                                                                                                                                                                                                                                                                                     |      |                    |  |  |
| Communicates post-treatment considerations to the patient, caregivers, and appropriate personnel                                                                                                                                                                                                                                                                                                                                                                                   |      |                    |  |  |

**APPENDIX B. Clinical Practicum Evaluation: Part II**

| Note the appropriate column to indicate that the nurse has satisfactorily performed the listed activities. Under Comments, provide examples of how the nurse met each objective or performed each activity. Include plans for remediation as applicable.                                                                                                                                                                                                                                                                                       |               |  |  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|--|--|
| Objective/Activity                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Date/Initials |  |  |
| Participates in interprofessional care planning with physicians, nurses, and other healthcare professionals (e.g., homecare, dietary), providing interventions specific to individual patient needs<br>Comments:                                                                                                                                                                                                                                                                                                                               |               |  |  |
| Provides individualized patient and family education and verifies understanding of the treatment, short- and long-term side effects, symptom management, and monitoring to occur with treatment<br>Comments:                                                                                                                                                                                                                                                                                                                                   |               |  |  |
| Documents pretreatment system review, including assessment of symptoms and response to previous therapy<br>Comments:                                                                                                                                                                                                                                                                                                                                                                                                                           |               |  |  |
| Describes anticipated complications and side effects of antineoplastic therapy on body systems<br><ul style="list-style-type: none"> <li>• Cardiovascular</li> <li>• Dermatologic</li> <li>• Endocrine</li> <li>• Gastrointestinal and nutritional</li> <li>• Genitourinary and renal</li> <li>• Head, ears, eyes, nose, and throat</li> <li>• Hematologic and lymphatic</li> <li>• Immunologic</li> <li>• Neurologic and musculoskeletal</li> <li>• Psychosocial</li> <li>• Pulmonary</li> <li>• Reproductive and sexual</li> </ul> Comments: |               |  |  |
| Identifies evidence-based interventions for complications and side effects of therapy<br>Comments:                                                                                                                                                                                                                                                                                                                                                                                                                                             |               |  |  |
| Documents patient response and care according to institutional policy and procedures<br>Comments:                                                                                                                                                                                                                                                                                                                                                                                                                                              |               |  |  |
| Identifies and takes nursing action to prevent or manage potential or actual infusion reactions<br>Comments:                                                                                                                                                                                                                                                                                                                                                                                                                                   |               |  |  |
| Uses appropriate safe handling precautions in the preparation, handling, and disposal of hazardous drugs<br>Comments:                                                                                                                                                                                                                                                                                                                                                                                                                          |               |  |  |
| Demonstrates knowledge and skill in the assessment, management, and follow-up care of infiltrations and extravasations<br>Comments:                                                                                                                                                                                                                                                                                                                                                                                                            |               |  |  |
| Assesses patients for the most appropriate type of vascular access device (peripheral or central) based on type and duration of intended therapy<br>Comments:                                                                                                                                                                                                                                                                                                                                                                                  |               |  |  |
| Demonstrates safe and appropriate use of equipment (e.g., closed-system drug-transfer devices, IV pumps, personal protective equipment) used in antineoplastic therapy administration.<br>Comments:                                                                                                                                                                                                                                                                                                                                            |               |  |  |
| Supports clinical research, as applicable to setting, by ensuring patient understanding of clinical trials, administering research drugs, documenting patient response to treatment, and contacting the research team as indicated<br>Comments:                                                                                                                                                                                                                                                                                                |               |  |  |

**APPENDIX C. Sample Chemotherapy Order Template**

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                            |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Breast Cancer</b><br><b>AC (DOXOrubicin/Cyclophosphamide) Every 21 Days followed by DOCEtaxel Every 21 Days + Trastuzumab</b><br><i>AC (DOXOrubicin/Cyclophosphamide) Every 21 Days Course</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                            |
| <b>INDICATION:</b><br>HER2 positive:<br>Neoadjuvant or<br>Adjuvant                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | <b>REFERENCES:</b><br>1. NCCN Guidelines® for Breast Cancer V2.2022.<br>2. Slamon D, et al. <i>N Engl J Med.</i> 2011;365(14):1273-83.<br>3. Joensuu H, et al. <i>N Engl J Med.</i> 2006;354(8):809-20.<br>4. Tolane S.M., et al. <i>N Engl J Med.</i> 2015;372(2):134-41. | <b>NCCN SUPPORTIVE CARE:</b><br>1. <i>Emetic risk:</i> Day 1 High<br>2. <i>Febrile Neutropenia Risk:</i> Refer to Myeloid Growth Factor algorithms in the NCCN Guidelines for Hematopoietic Growth Factors |
| <b>CHEMOTHERAPY REGIMEN</b><br><i>21-day cycle for 4 cycles</i> <ul style="list-style-type: none"> <li>• <b>DOXOrubicin</b> 60 mg/m<sup>2</sup> IV push on Day 1 <ul style="list-style-type: none"> <li>– See <i>Safety Parameters and Special Instructions</i> for information on slow IV Push administration.</li> </ul> </li> <li>• <b>Cyclophosphamide</b> 600 mg/m<sup>2</sup> IV over 30 minutes on Day 1 <ul style="list-style-type: none"> <li>– Oral hydration is strongly encouraged with cyclophosphamide; poorly hydrated patients may need supplemental IV hydration. Patients should attain combined oral and IV hydration of 2000 – 3000 mL/day on day of chemotherapy. See <i>Other Supportive Therapy</i> for example of IV hydration.</li> </ul> </li> </ul> <p><b>This course is 4 cycles of AC (DOXOrubicin and cyclophosphamide) Every 21 Days. DOCEtaxel Every 21 Days and Trastuzumab course is initiated following completion of this course. Please see Order Template BRS27b for DOCEtaxel Every 21 Days and Trastuzumab course.</b></p> <b>SUPPORTIVE CARE</b><br><b>Antiemetic Therapy</b><br>Scheduled prophylactic antiemetic therapy should be given for prevention of acute and delayed nausea and vomiting based on the emetic risk of the chemotherapy regimen. This may include antiemetic therapy given on the days following chemotherapy. For more information on emetic prophylaxis, refer to the NCCN Guidelines for Antiemesis and Appendix D to the NCCN Chemotherapy Order Templates.<br><b>PRN for breakthrough:</b> All patients should be provided with at least one medication for breakthrough emesis. Please consult the NCCN Guidelines for Antiemesis for appropriate antiemetic therapy.<br><b>Other Supportive Therapy</b> <ul style="list-style-type: none"> <li>• For cyclophosphamide: <i>Example of recommended hydration:</i> Sodium chloride 0.9% infused IV at a rate of 1.5 – 3 mL/kg/hour for a total of 500 mL on day of chemotherapy.</li> </ul> <b>MONITORING AND HOLD PARAMETERS</b> <ul style="list-style-type: none"> <li>• CBC with differential should be monitored as clinically indicated for potential dose modification.</li> <li>• For DOXOrubicin: <ul style="list-style-type: none"> <li>– This agent is an anthracycline. Cumulative anthracycline dosage should be monitored.</li> <li>– Ejection fraction should be monitored prior to initiation of treatment and as clinically indicated.</li> <li>– Liver function should be monitored prior to each cycle and as clinically indicated for potential dose modification or discontinuation.</li> </ul> </li> <li>• For cyclophosphamide: Renal function should be monitored as clinically indicated for potential dose modification or discontinuation.</li> </ul> <b>SAFETY PARAMETERS AND SPECIAL INSTRUCTIONS</b> <ul style="list-style-type: none"> <li>• For DOXOrubicin: <ul style="list-style-type: none"> <li>– <b>This agent is a vesicant OR an irritant with vesicant properties.</b></li> <li>– This agent is administered IV push. The preferred IV push method for a vesicant is administration through the side port of a freely flowing IV.</li> <li>– Secondary malignancies have been associated with this drug. Review drug package insert for additional information.</li> <li>– Central venous access is recommended for administration of this agent.</li> </ul> </li> <li>• For cyclophosphamide: Secondary malignancies have been associated with this drug. Review drug package insert for additional information.</li> </ul> |                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                            |

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# APPENDIX D. Antineoplastic Treatment Safety Checklist

|                                                              |                                                                                                                                                                                                           |
|--------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| √                                                            | Criteria                                                                                                                                                                                                  |
|                                                              | Patient, parent, and/or caregiver have received written and verbal education.                                                                                                                             |
|                                                              | Patient reports understanding of treatment plan and elects to proceed.                                                                                                                                    |
|                                                              | Confirm presence of informed consent documentation (as applicable to practice setting).                                                                                                                   |
| <b>Pretreatment Assessment</b>                               |                                                                                                                                                                                                           |
|                                                              | Obtain vital signs.                                                                                                                                                                                       |
|                                                              | Ensure measured height and weight are current and obtained and documented in metric units.                                                                                                                |
|                                                              | Review allergies.                                                                                                                                                                                         |
|                                                              | Review response to previous treatments, including reactions and treatment toxicities.                                                                                                                     |
|                                                              | Update medication list and reconcile as needed.                                                                                                                                                           |
|                                                              | Perform and record physical assessment including a pain assessment.                                                                                                                                       |
|                                                              | Perform psychosocial assessment; initiate referrals and resources if necessary.                                                                                                                           |
|                                                              | Review laboratory values relevant to treatment.                                                                                                                                                           |
|                                                              | Prepare for potential complications, including infusion reaction, infiltration, and extravasation.                                                                                                        |
| <b>Treatment plan is noted in medical record.</b>            |                                                                                                                                                                                                           |
|                                                              | Document the diagnosis, indication for treatment, antineoplastic agents to be used, doses (with calculation methodology), schedule, and dose modification and rationale for modification (if applicable). |
| <b>Antineoplastic orders include the following elements:</b> |                                                                                                                                                                                                           |
|                                                              | Orders signed and activated per institutional policy                                                                                                                                                      |
|                                                              | Doses consistent with standard regimens or research protocols approved by the practice or institution. Rationale for exception orders is documented.                                                      |
|                                                              | Patient name and second identifier                                                                                                                                                                        |
|                                                              | Cycle number and day of cycle or arm, phase per research protocol                                                                                                                                         |
|                                                              | Date order was written and date of drug administration                                                                                                                                                    |
|                                                              | All medications identified by generic name, following abbreviation standards                                                                                                                              |
|                                                              | Cumulative dose calculated for drugs that have an upper lifetime dose limit                                                                                                                               |
|                                                              | Multiday continuous infusions include total daily dose and total multiday hours of infusion.                                                                                                              |
|                                                              | Supportive care treatments are ordered (e.g., hydration, antiemetics, growth factors).                                                                                                                    |
|                                                              | Required filter or special tubing                                                                                                                                                                         |
|                                                              | Sequence of drug administration                                                                                                                                                                           |

(Continued on next page)

**APPENDIX D. Antineoplastic Treatment Safety Checklist (Continued)**

|                                                                                                                                                             |                                                                                                                                                                                              |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Two people approved by the healthcare setting to prepare or administer chemotherapy independently perform each of the following three safety checks:</b> |                                                                                                                                                                                              |
| <b>1. Before preparation</b>                                                                                                                                |                                                                                                                                                                                              |
|                                                                                                                                                             | Verify two patient identifiers, drug name, dose, route, rate, calculations for dosing, treatment cycle, and day of cycle.                                                                    |
| <b>2. Upon preparation of parenteral antineoplastic therapy</b>                                                                                             |                                                                                                                                                                                              |
|                                                                                                                                                             | Verify drug vial, drug concentration, drug volume or weight, diluent type and volume, drug stability, need for refrigeration, administration fluid, volume and tubing, and filter if needed. |
| <b>3. Before administration, verify:</b>                                                                                                                    |                                                                                                                                                                                              |
|                                                                                                                                                             | Drug name                                                                                                                                                                                    |
|                                                                                                                                                             | Drug dose                                                                                                                                                                                    |
|                                                                                                                                                             | Volume                                                                                                                                                                                       |
|                                                                                                                                                             | Route of administration                                                                                                                                                                      |
|                                                                                                                                                             | Sequence of drug administration                                                                                                                                                              |
|                                                                                                                                                             | Expiration date and/or time                                                                                                                                                                  |
|                                                                                                                                                             | Appearance and physical integrity of drug                                                                                                                                                    |
|                                                                                                                                                             | Rate of administration                                                                                                                                                                       |
|                                                                                                                                                             | Patient identification using two patient identifiers in the presence of the patient                                                                                                          |
|                                                                                                                                                             | Rate of infusion (infusion pump settings)                                                                                                                                                    |

*Note.* Based on information from Neuss, M.N., Gilmore, T.R., Belderson, K.M., Billett, A.L., Conti-Kalchik, T., Harvey, B.E., ... Polovich, M. (2016). 2016 updated American Society of Clinical Oncology/Oncology Nursing Society chemotherapy administration safety standards, including standards for pediatric oncology. *Journal of Oncology Practice*, 12(12), 1262–1271. <https://doi.org/10.1200/JOP.2016.017905>.

## APPENDIX E. Consent for Antineoplastic Drug Treatment

Patient Name: \_\_\_\_\_ Date: \_\_\_\_\_

Diagnosis: \_\_\_\_\_

Treatment Medications: \_\_\_\_\_

**Possible side effects may include any of the following or a combination of the following:**

- |                                        |                                       |                                     |
|----------------------------------------|---------------------------------------|-------------------------------------|
| • Allergic and allergic-like reactions | • Kidney damage                       | • Nausea or vomiting                |
| • Anemia                               | • Light and temperature sensitivity   | • Numbness or tingling              |
| • Cognitive impairments                | • Liver damage                        | • Risk of infection                 |
| • Constipation                         | • Loss of appetite                    | • Secondary cancer                  |
| • Diarrhea                             | • Low platelet count causing bleeding | • Skin and nail darkening           |
| • Dizziness                            | • Low white blood cell count          | • Skin rash                         |
| • Fatigue                              | • Lung damage                         | • Skin ulceration at injection site |
| • Forgetfulness                        | • Menopausal symptoms                 | • Sterility                         |
| • Hair loss                            | • Menstrual irregularities            | • Thyroid changes                   |
| • Hearing loss                         | • Mouth sores                         | • Weight gain or loss               |
| • Heart damage                         | • Muscle aching or weakness           |                                     |

**Unexpected side effects may occur in addition to those noted above. Cancer treatments can cause long-term toxicities. In rare instances, cancer treatment can cause life-threatening complications and death.**

Many anticancer drugs can be harmful to an unborn child. I understand that it is important to tell the doctor if I think I may be pregnant. It is important for both men and women who are being treated with these drugs and who are sexually active and fertile and who have a fertile partner to use a reliable form of birth control (birth control pills, a reliable barrier method, or a hormonal implant as recommended by a physician). I have discussed possible ways of preserving my fertility with my doctor, if applicable.

\_\_\_\_ (Patient Initials) A healthcare professional has provided and reviewed with me written information on the drugs I will receive. I HAVE HAD THE CHANCE TO ASK ANY QUESTIONS ABOUT THE DRUGS I WILL RECEIVE AND AM SATISFIED WITH THE INFORMATION PROVIDED.

My healthcare team has explained my treatment plan in detail. My doctor has discussed with me other methods of treating this disease and the risks and benefits of treatment. There is no guarantee that this treatment will give me the same results that other patients have received. If I change my mind and decide to stop treatment at any time, my doctor will continue to provide for my care in the future.

**I have read the above information. I understand the possible risks and benefits of the recommended treatment plan. I agree to accept the treatment and authorize Dr. \_\_\_\_\_ and his/her healthcare team to carry out the treatment plan.**

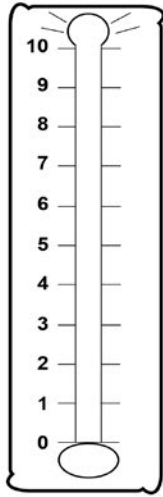
Patient Signature: \_\_\_\_\_ Date: \_\_\_\_\_

I have explained the expected response, side effects, and possibility of risks of the listed drugs to the above named patient.

Physician Signature: \_\_\_\_\_ Date: \_\_\_\_\_



## APPENDIX F. Distress Thermometer

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        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| <p><b>NCCN DISTRESS THERMOMETER</b><br/> Distress is an unpleasant experience of a mental, physical, social, or spiritual nature. It can affect the way you think, feel, or act. Distress may make it harder to cope with having cancer, its symptoms, or its treatment.</p> <p><b>Instructions:</b> Please circle the number (0–10) that best describes how much distress you have been experiencing in the past week, including today.</p> <div style="display: flex; align-items: center; justify-content: center;"> <div style="text-align: right; margin-right: 10px;"> <p><b>Extreme distress</b></p> <p><b>No distress</b></p> </div>  </div>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | <p><b>PROBLEM LIST</b><br/> Have you had concerns about any of the items below in the past week, including today? (Mark all that apply)</p> <table border="0"> <tr> <td style="vertical-align: top;"> <p><b>Physical Concerns</b></p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Pain</li> <li><input type="checkbox"/> Sleep</li> <li><input type="checkbox"/> Fatigue</li> <li><input type="checkbox"/> Tobacco use</li> <li><input type="checkbox"/> Substance use</li> <li><input type="checkbox"/> Memory or concentration</li> <li><input type="checkbox"/> Sexual health</li> <li><input type="checkbox"/> Changes in eating</li> <li><input type="checkbox"/> Loss or change of physical abilities</li> </ul> <p><b>Emotional Concerns</b></p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Worry or anxiety</li> <li><input type="checkbox"/> Sadness or depression</li> <li><input type="checkbox"/> Loss of interest or enjoyment</li> <li><input type="checkbox"/> Grief or loss</li> <li><input type="checkbox"/> Fear</li> <li><input type="checkbox"/> Loneliness</li> <li><input type="checkbox"/> Anger</li> <li><input type="checkbox"/> Changes in appearance</li> <li><input type="checkbox"/> Feelings of worthlessness or being a burden</li> </ul> <p><b>Social Concerns</b></p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Relationship with spouse or partner</li> <li><input type="checkbox"/> Relationship with children</li> <li><input type="checkbox"/> Relationship with family members</li> <li><input type="checkbox"/> Relationship with friends or coworkers</li> <li><input type="checkbox"/> Communication with health care team</li> <li><input type="checkbox"/> Ability to have children</li> </ul> </td> <td style="vertical-align: top;"> <p><b>Practical Concerns</b></p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Taking care of myself</li> <li><input type="checkbox"/> Taking care of others</li> <li><input type="checkbox"/> Work</li> <li><input type="checkbox"/> School</li> <li><input type="checkbox"/> Housing</li> <li><input type="checkbox"/> Finances</li> <li><input type="checkbox"/> Insurance</li> <li><input type="checkbox"/> Transportation</li> <li><input type="checkbox"/> Child care</li> <li><input type="checkbox"/> Having enough food</li> <li><input type="checkbox"/> Access to medicine</li> <li><input type="checkbox"/> Treatment decisions</li> </ul> <p><b>Spiritual or Religious Concerns</b></p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Sense of meaning or purpose</li> <li><input type="checkbox"/> Changes in faith or beliefs</li> <li><input type="checkbox"/> Death, dying or afterlife</li> <li><input type="checkbox"/> Conflict between beliefs and cancer treatments</li> <li><input type="checkbox"/> Relationship with the sacred</li> <li><input type="checkbox"/> Ritual or dietary needs</li> </ul> <p><b>Other Concerns:</b></p> <hr/> <hr/> <hr/> </td> </tr> </table> | <p><b>Physical Concerns</b></p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Pain</li> <li><input type="checkbox"/> Sleep</li> <li><input type="checkbox"/> Fatigue</li> <li><input type="checkbox"/> Tobacco use</li> <li><input type="checkbox"/> Substance use</li> <li><input type="checkbox"/> Memory or concentration</li> <li><input type="checkbox"/> Sexual health</li> <li><input type="checkbox"/> Changes in eating</li> <li><input type="checkbox"/> Loss or change of physical abilities</li> </ul> <p><b>Emotional Concerns</b></p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Worry or anxiety</li> <li><input type="checkbox"/> Sadness or depression</li> <li><input type="checkbox"/> Loss of interest or enjoyment</li> <li><input type="checkbox"/> Grief or loss</li> <li><input type="checkbox"/> Fear</li> <li><input type="checkbox"/> Loneliness</li> <li><input type="checkbox"/> Anger</li> <li><input type="checkbox"/> Changes in appearance</li> <li><input type="checkbox"/> Feelings of worthlessness or being a burden</li> </ul> <p><b>Social Concerns</b></p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Relationship with spouse or partner</li> <li><input type="checkbox"/> Relationship with children</li> <li><input type="checkbox"/> Relationship with family members</li> <li><input type="checkbox"/> Relationship with friends or coworkers</li> <li><input type="checkbox"/> Communication with health care team</li> <li><input type="checkbox"/> Ability to have children</li> </ul> | <p><b>Practical Concerns</b></p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Taking care of myself</li> <li><input type="checkbox"/> Taking care of others</li> <li><input type="checkbox"/> Work</li> <li><input type="checkbox"/> School</li> <li><input type="checkbox"/> Housing</li> <li><input type="checkbox"/> Finances</li> <li><input type="checkbox"/> Insurance</li> <li><input type="checkbox"/> Transportation</li> <li><input type="checkbox"/> Child care</li> <li><input type="checkbox"/> Having enough food</li> <li><input type="checkbox"/> Access to medicine</li> <li><input type="checkbox"/> Treatment decisions</li> </ul> <p><b>Spiritual or Religious Concerns</b></p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Sense of meaning or purpose</li> <li><input type="checkbox"/> Changes in faith or beliefs</li> <li><input type="checkbox"/> Death, dying or afterlife</li> <li><input type="checkbox"/> Conflict between beliefs and cancer treatments</li> <li><input type="checkbox"/> Relationship with the sacred</li> <li><input type="checkbox"/> Ritual or dietary needs</li> </ul> <p><b>Other Concerns:</b></p> <hr/> <hr/> <hr/> |
| <p><b>Physical Concerns</b></p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Pain</li> <li><input type="checkbox"/> Sleep</li> <li><input type="checkbox"/> Fatigue</li> <li><input type="checkbox"/> Tobacco use</li> <li><input type="checkbox"/> Substance use</li> <li><input type="checkbox"/> Memory or concentration</li> <li><input type="checkbox"/> Sexual health</li> <li><input type="checkbox"/> Changes in eating</li> <li><input type="checkbox"/> Loss or change of physical abilities</li> </ul> <p><b>Emotional Concerns</b></p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Worry or anxiety</li> <li><input type="checkbox"/> Sadness or depression</li> <li><input type="checkbox"/> Loss of interest or enjoyment</li> <li><input type="checkbox"/> Grief or loss</li> <li><input type="checkbox"/> Fear</li> <li><input type="checkbox"/> Loneliness</li> <li><input type="checkbox"/> Anger</li> <li><input type="checkbox"/> Changes in appearance</li> <li><input 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type="checkbox"/> Child care</li> <li><input type="checkbox"/> Having enough food</li> <li><input type="checkbox"/> Access to medicine</li> <li><input type="checkbox"/> Treatment decisions</li> </ul> <p><b>Spiritual or Religious Concerns</b></p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Sense of meaning or purpose</li> <li><input type="checkbox"/> Changes in faith or beliefs</li> <li><input type="checkbox"/> Death, dying or afterlife</li> <li><input type="checkbox"/> Conflict between beliefs and cancer treatments</li> <li><input type="checkbox"/> Relationship with the sacred</li> <li><input type="checkbox"/> Ritual or dietary needs</li> </ul> <p><b>Other Concerns:</b></p> <hr/> <hr/> <hr/>                                                                                                                                                                                                                                                                                         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Note: All recommendations are category 2A unless otherwise indicated.  
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Note. Reproduced with permission from *NCCN Distress Thermometer and Problem List for Patients* [v.1.2022]. © 2022 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines<sup>®</sup> and illustrations herein may not be reproduced in any form for any purpose without the express written permission of NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to [NCCN.org](http://NCCN.org). The NCCN Guidelines are a work in progress that may be refined as often as new significant data becomes available.

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# APPENDIX G. Hazardous Drug Administration Safe Handling Checklist

| Name: _____ Date of Review and Exam: _____                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |     |    |          |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|----|----------|
| PRIOR TO ADMINISTRATION                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Yes | No | Initials |
| 1. Gather equipment required for drug administration.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |     |    |          |
| 2. Select appropriate gloves for hazardous drug (HD) administration.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |     |    |          |
| 3. Select appropriate gown for HD administration.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |     |    |          |
| 4. Identify situations when mask and face protection are required.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |     |    |          |
| 5. Gather administration supplies including closed-system drug-transfer devices (CSTDs) that are needed for administration of HD, when the dosage form allows.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |     |    |          |
| 6. Locate HD spill kit.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |     |    |          |
| 7. Obtain hazardous waste container.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |     |    |          |
| 8. Receive drug(s) from pharmacy in sealed bag.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |     |    |          |
| ADMINISTRATION                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |     |    |          |
| 1. Wash hands and don personal protective equipment before opening drug delivery bag.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |     |    |          |
| 2. Visually inspect the contents of the delivery bag for leaks.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |     |    |          |
| 3. For IV infusions <ul style="list-style-type: none"> <li>• Ensure tubing is primed with a non-HD solution. Back-priming is acceptable when using secondary tubing for administration. For HDs with high risk of reaction that have the tubing primed with HDs, pharmacy must prime tubing within a containment primary engineering controls (C-PEC) and deliver with a CSTD on the end of the tubing.</li> <li>• Work below eye level.</li> <li>• Utilize CSTD when the dosage form allows.</li> <li>• Utilize plastic backed absorbent pad under work area. Remove cap from IV tubing/CSTD and connect to patient's IV device with CSTD.</li> <li>• Tighten locking connections.</li> <li>• Remove outer gloves prior to programming pump.</li> <li>• Doff personal protective equipment and wash hands with soap and water.</li> <li>• When HD administration is complete, don personal protective equipment and discontinue IV bag with tubing intact (do not unspike bag, or reuse tubing).</li> <li>• Utilize gauze pads and a closed cap (for end of tubing to prevent dripping) when disconnecting from patient's IV device.</li> <li>• Remove outer gloves and discard.</li> <li>• Discard HD and HD administration set in HD waste container without touching surfaces. Tip: hold HD supplies in one hand and use clean inner glove to open doors, if traveling to a waste container.</li> </ul> |     |    |          |
| 4. For IV push medications <ul style="list-style-type: none"> <li>• Utilize CSTD when the dosage form allows.</li> <li>• Utilize plastic backed absorbent pad under work area. Remove cap from IV tubing and connect to patient's IV device.</li> <li>• Tighten locking connection.</li> <li>• When complete, remove outer gloves.</li> <li>• Do not recap needle.</li> <li>• Discard HD and HD storage container in HD waste container without touching surfaces. Tip: hold HD supplies in one hand and use clean inner glove to open doors, if traveling to a waste container.</li> <li>• Discard syringe-needle unit in puncture-proof container.</li> <li>• Doff personal protective equipment and wash hands with soap and water.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |     |    |          |

(Continued on next page)

**APPENDIX G. Hazardous Drug Administration Safe Handling Checklist (Continued)**

| ADMINISTRATION (Cont.)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Yes | No | Initials |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|----|----------|
| 5. For intramuscular/subcutaneous injections <ul style="list-style-type: none"> <li>Utilize CSTD when dosage form allows.</li> <li>Attach needle to syringe.</li> <li>Utilize plastic backed absorbent pad under work area.</li> <li>Tighten locking connection.</li> <li>When complete, do not recap needle.</li> <li>Discard HD and HD storage container in HD waste container without touching surfaces. Tip: hold HD supplies in one hand and use clean inner glove to open doors, if traveling to a waste container.</li> <li>Discard syringe-needle unit in puncture-proof container.</li> <li>Doff personal protective equipment and wash hands with soap and water.</li> </ul> |     |    |          |
| 6. For oral drugs (tablets/capsules) <ul style="list-style-type: none"> <li>If using bar code technology, scan medication prior to removing medication from packaging.</li> <li>Don gloves.</li> <li>Open unit-dose package and place into medicine cup (avoid touching drug or inside of package).</li> <li>Avoid touching tablets/capsules.</li> <li>Doff gloves and wash hands with soap and water.</li> </ul>                                                                                                                                                                                                                                                                      |     |    |          |
| 7. For oral drugs in liquid form <ul style="list-style-type: none"> <li>Obtain drug in final form in appropriate oral syringe or appropriate container.</li> <li>Don double gloves, gown, and mask with face protection.</li> <li>Use plastic-backed absorbent pad during administration.</li> <li>Discard syringe in hazardous waste container after administration.</li> <li>Doff personal protective equipment and wash hands with soap and water.</li> </ul>                                                                                                                                                                                                                       |     |    |          |
| POST ADMINISTRATION                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |     |    |          |
| 1. Don personal protective equipment.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |     |    |          |
| 2. Seal hazardous drug–contaminated supplies in sealable plastic bag for transport to hazardous waste container.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |     |    |          |
| 3. Remove outer gloves before touching equipment.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |     |    |          |
| 4. Place sealed plastic bag in hazardous waste container.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |     |    |          |
| 5. Close lid on waste container.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |     |    |          |
| 6. Clean equipment per manufacturer guidelines.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |     |    |          |
| 7. Remove and discard gown, and inner gloves.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |     |    |          |
| 8. Wash hands thoroughly with soap and water.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |     |    |          |
| 9. If a mask and face shield was used, don clean gloves to remove and then repeat hand washing after glove removal.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |     |    |          |
| 10. If the patient is on airborne precautions and full personal protective equipment with a powered air purifying respirator (PAPR)/cartridge mask or N95 is used, a new pair of gloves should be worn to remove the PAPR/cartridge mask or N95 and it should be placed on a plastic-backed pad, gloves removed, and hands washed. A final pair of gloves should be used to clean the equipment per manufacturer's guidelines and then remove gloves and wash hands again.                                                                                                                                                                                                             |     |    |          |

## APPENDIX H. Extravasation



Photo 1. Erythema of site of port extravasation of doxorubicin (February 14)



Photo 2. Beginning of skin necrosis (February 28)



Photo 3. Area of extravasation following debridement (March 18)



Photo 4. Granulation of outer areas of debrided area (June 5)



Photo 5. Ten months following extravasation, healing of area and formation of scars (December 10)



Photo 6. Severe tissue necrosis secondary to vesicant extravasation

Note. Photos 1–5 from "Chemotherapy Extravasation From Implanted Ports," by L. Schulmeister and D. Camp-Sorrell, 2000, *Oncology Nursing Forum*, 27(3), p. 534. Copyright 2000 by Oncology Nursing Society. Reprinted with permission. Photo 6 courtesy of Rita Wickham, RN, PhD, AOCN®. Used with permission.

**APPENDIX I. Vesicant Drug Extravasation Record**

| Patient: _____ Date of infiltration: _____ Time: _____                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                            |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Today's date: _____                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                            |
| Drug: _____ Dilution (mg/ml): _____                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                            |
| Estimated amount infiltrated: _____                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                            |
| Vascular Access                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Infusion Method                                                                                                                                                                                                                                                                                 | Pretreatment Assessment                                                                                                                                                                                                                                    |
| <input type="checkbox"/> Peripheral IV<br>Location: _____<br><input type="checkbox"/> Peripherally inserted central catheter<br><input type="checkbox"/> Implanted port<br>Needle size and length: _____<br><input type="checkbox"/> Tunneled catheter<br><input type="checkbox"/> Other                                                                                                                                                                                                                                               | <input type="checkbox"/> IV push via side-arm of free-flowing IV<br><input type="checkbox"/> Direct IV push<br><input type="checkbox"/> Minibag infusion<br><input type="checkbox"/> Continuous infusion<br><br>Infusion pump used?<br><input type="checkbox"/> Yes <input type="checkbox"/> No | Location: _____<br><br>Type and size of needle/catheter: _____<br>_____<br><br>Description and quality of blood return: _____<br>_____<br><br>Comments: _____<br>_____<br><br><b>Consider timed and dated photograph of site to add to medical record.</b> |
| <b>Description:</b><br>Include topical cooling/heating applied, treatments, antidotes used, measurements of site, edema, and/or redness. Assess extremity for range of motion and discomfort with movement.<br><br>Situation: _____<br><br>Background: _____<br>_____<br>_____<br><br>Assessment (include photos): _____<br>_____<br>_____<br><br>Recommendations: _____<br>_____<br>_____<br><br>Authorized prescriber notified: _____<br><br>Patient/Caregiver instructions: _____<br>_____<br><br>Comments: _____<br>_____<br>_____ |                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                            |
| <b>Consultations:</b><br><input type="checkbox"/> Plastic surgery      Date: _____<br><input type="checkbox"/> Physical therapy      Date: _____<br><input type="checkbox"/> Other: _____<br>_____<br>_____<br>_____                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                 | <b>Follow-up:</b><br>Include return appointments, patient instructions on skin assessment, temperature monitoring, and reporting of pain.<br>_____<br>_____<br>_____                                                                                       |
| Notes: _____<br>_____<br>_____<br>_____                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                            |
| Signature: _____ Date: _____                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                            |

# Index

*The letter f after a page number indicates that relevant content appears in a figure; the letter t, in a table.*

5-fluorouracil (5-FU), 79t–80t  
 cardiotoxicity of, 501t  
 diarrhea from, 448  
 hepatotoxicity of, 587t  
 as irritant, 368t, 369  
 ocular toxicity of, 759t  
 5-HT<sub>3</sub> receptor antagonists, for CINV, 432–434, 439  
 6-mercaptopurine (6-MP), 80t  
 hepatotoxicity of, 587t  
<sup>90</sup>Y-ibritumomab tiuxetan, 222t–223t, 284, 285  
 infusion reaction from, 377t

## A

abemaciclib, 114t, 193  
 pulmonary toxicity of, 551t  
 abiraterone, 104t, 109  
 cardiotoxicity of, 527t  
 hepatotoxicity of, 603t  
 absolute neutrophil count (ANC), 405, 410  
 acalabrutinib, 114t–115t, 193  
 pulmonary toxicity of, 551t  
*Access Device Standards of Practice for Oncology Nursing*, 17, 310  
 acneiform eruptions, 658t, 669–670, 676t  
 acquired drug resistance, 44  
 acryl erythema, 658t–659t  
 acute cholestasis, 604  
 acute hepatocellular injury, 604  
 acute kidney injury (AKI), 615, 616f, 623–625  
 acute onset CINV, 428, 432–434  
 acute promyelocytic leukemia (APL)  
   treatment-related differentiation syndrome (DS), 574–575  
 adaptive immunity, 204, 204f, 205t, 206f  
 adherence, to treatment, 44–48, 45t, 48f, 309  
 adjuvant therapy, defined, 37  
 ado-trastuzumab emtansine, 217t  
   cardiotoxicity of, 523t  
   hepatotoxicity of, 601t–602t  
   infusion reaction from, 372t  
   as irritant, 367t, 369  
   ocular toxicity of, 763t  
 adrenal cancer, hormone therapy for, 107  
 adrenal insufficiency, 698–699  
 adrenolytics, 102t, 110

adverse events  
   defined, 48  
   grading of, 48–49, 49t (*See also Common Terminology Criteria for Adverse Events*)  
 afatinib, 115t  
   cardiotoxicity of, 504t  
   genitourinary toxicity of, 619t  
   hepatotoxicity of, 591t  
   ocular toxicity from, 764t  
   pulmonary toxicity of, 551t  
 Agency for Healthcare Research and Quality (AHRQ), on health literacy, 21  
 aldesleukin, 246t–247t  
   cardiotoxicity of, 521t–522t  
   genitourinary toxicity of, 622t  
   hepatotoxicity of, 601t  
   pulmonary toxicity of, 560t  
 alectinib, 113, 116t  
   cardiotoxicity of, 504t  
   genitourinary toxicity of, 619t  
   hepatotoxicity of, 592t  
   ocular toxicity from, 765t  
   pulmonary toxicity of, 551t  
 alemtuzumab, 261t  
   cardiotoxicity of, 524t  
   hepatotoxicity of, 602t  
   infusion reaction from, 372t  
   pulmonary toxicity of, 565t  
 alimentary tract mucositis, 467. *See also* mucositis  
 alkalinization, for TLS management, 629  
 alkylating agents, 68, 69t–75t, 97f. *See also* specific agents  
   cardiotoxicity of, 494t–496t  
   cutaneous toxicities of, 657  
   extravasation of, 363t  
   genitourinary toxicity of, 617t–618t  
   hepatotoxicity of, 585t–586t  
   ocular toxicity of, 758t  
   peripheral neuropathy from, 722t  
   pulmonary toxicity of, 546t–547t  
   second cancer risk with, 778  
   sexual dysfunction from, 645  
 all-trans-retinoic acid, 87t  
   pulmonary toxicity of, 549t  
 alopecia, 660t, 676t, 677  
   clinical manifestations of, 678

incidence/risk factors of, 678, 679t  
 management of, 678–680  
 pathophysiology of, 677–678  
 patient education on, 680–681  
 alpelisib, 116t–117t  
   pulmonary toxicity of, 552t  
 alprazolam, for CINV, 436t  
 American Cancer Society, 24  
   on clinical trial participation, 54  
 American College of Surgeons, Commission on Cancer (CoC)  
   accreditation standards, 17  
   safety monitoring by, 9  
 American Nurses Association, code of ethics of, 16  
 American Society of Clinical Oncology (ASCO), 24  
   on CINV management, 432–434  
   on clinical trial participation, 54  
   on immune-related adverse events, 276  
   on older adult patients, 298  
   on psychosocial assessment, 303  
   safety monitoring by, 9  
   safety standards of, 3, 16–17  
   on survival/QoL, 41  
   treatment summary templates, 9  
 amifostine, for proctitis prevention, 472, 473t  
 amivantamab-vmjw, 271t  
   pulmonary toxicity of, 568t  
 anagen effluvium, 677–678. *See also* alopecia  
 anaphylaxis, 383–387, 388t–389t, 390f, 390t. *See also* infusion-related reactions  
 anaplastic lymphoma kinase (ALK) inhibitors, 113  
   diarrhea from, 448  
 anastrozole, 103t  
   ocular toxicity of, 761t  
 androgen receptor inhibitors, 102t–103t, 106–107. *See also* specific agents  
   cardiotoxicity of, 527t  
   hepatotoxicity of, 603t  
 anemia, 405, 406t, 418–420, 741  
   incidence of, 418  
   management of, 419–420, 420t  
   risk factors for, 418–419  
 angiogenesis, 209–210  
 Ann Arbor staging system, 33



- anorexia/cachexia, 442  
 assessment of, 443–444  
 clinical manifestations of, 443  
 grading of, 444, 445t  
 incidence of, 443  
 management of, 444–445  
 pathophysiology of, 442  
 patient education on, 445–446  
 risk factors for, 443  
 types of, 442–443
- anthracyclines, 84t–87t, 294. *See also specific agents*  
 cardiotoxicity of, 496t–500t, 535–536  
 diarrhea from, 448  
 extravasation of, 359, 363t, 365  
 hepatotoxicity of, 588t–589t
- antiandrogens, 102t–103t, 106–109. *See also specific agents*
- antibody-drug conjugates, 214t–222t, 283–284.  
*See also specific agents*  
 genitourinary toxicity of, 622t  
 pulmonary toxicity of, 567t–568t
- anti-CD20 antibody, 258t, 294
- anti-CD38 antibody, 255t
- anticholinergics  
 for diarrhea, 456t  
 fatigue from, 707t
- anticipatory CINV, 428–429, 432
- anticonvulsants, fatigue from, 707t
- antidepressants, and cancer-related fatigue, 707t, 709
- anti-EGFR antibodies, 257t, 259t
- antiemetics  
 fatigue from, 707t  
 for nausea/vomiting, 431–432, 477t
- antigen recognition, by immune system, 208
- antihistamines, fatigue from, 707t
- antimetabolites, 75t–82t, 97. *See also specific agents*  
 cardiotoxicity of, 500t–502t  
 cutaneous toxicities of, 657  
 endocrine toxicities from, 686t  
 genitourinary toxicity of, 618t–619t  
 hepatotoxicity of, 586t–588t  
 ocular toxicity of, 758t–759t  
 pulmonary toxicity of, 547t–548t  
 sexual dysfunction from, 645
- antimotility agents, for diarrhea, 455t
- anti-RANK antibody, 256t
- antitumor antibiotics, 83t–87t, 97, 294. *See also specific agents*  
 cardiotoxicity of, 502t  
 cutaneous toxicities of, 657  
 endocrine toxicities from, 686t  
 extravasation of, 364t  
 genitourinary toxicity of, 619t  
 hepatotoxicity of, 588t–589t  
 ocular toxicity of, 759t–760t  
 pulmonary toxicity of, 548t  
 sexual dysfunction from, 645
- anti-VEGFR2 antibody, 259t–260t
- anxiolytics, fatigue from, 707t
- apalutamide, 102t–103t
- apoptosis, inhibition of, 44
- aprepitant, for CINV, 439t
- aromatase inhibitors, 103t–104t, 109. *See also specific agents*
- arsenic trioxide, 88t, 97
- cardiotoxicity of, 504t
- genitourinary toxicity of, 619t
- hepatotoxicity of, 589t
- pulmonary toxicity of, 549t
- asciminib, 113, 117t–118t
- ASCO/ONS *Chemotherapy Administration Safety Standards*, 3
- aseptic meningitis, 718t, 733
- asparaginase, 88t, 97  
 endocrine toxicities from, 686t  
 hepatotoxicity of, 589t
- atezolizumab, 232t–233t  
 cardiotoxicity of, 518t  
 endocrine toxicities from, 689t  
 hepatotoxicity of, 600t  
 infusion reaction from, 372t  
 pulmonary toxicity of, 557t
- atrial fibrillation, 493, 528
- atropine, for diarrhea, 454–455, 455t, 456t
- atypical antipsychotics, for CINV, 432, 436t
- AUC dosing calculation, 304
- autologous cellular immunotherapy, 247t  
 cardiotoxicity of, 526t
- autonomy, 16, 17t
- avapritinib, 118t
- avelumab, 234t  
 cardiotoxicity of, 518t  
 endocrine toxicities from, 689t  
 hepatotoxicity of, 600t  
 infusion reaction from, 372t  
 pulmonary toxicity of, 558t
- axicabtagene ciloleucel, 235t–236t, 277  
 cardiotoxicity of, 519t  
 pulmonary toxicity of, 568t
- axitinib, 119t, 198  
 cardiotoxicity of, 505t  
 endocrine toxicities from, 686t  
 hepatotoxicity of, 592t  
 ocular toxicity from, 764t
- azacitidine, 75t  
 cardiotoxicity of, 496t  
 genitourinary toxicity of, 618t
- ## B
- bacillus Calmette Guérin (BCG), 326
- barbiturates, fatigue from, 707t
- basophils, 408t
- B-cell aplasia, 279–280
- B-cell receptor pathway inhibitors, 193
- B cells, 205–207, 408t
- BCL2 protein, 197
- BCR-ABL1 TKIs, 113
- Beau lines, 659t
- bed linens, safe handling of, 351
- belantamab mafodotin-blmf, 216t, 756
- belinostat, 120t, 195  
 genitourinary toxicity of, 619t  
 hepatotoxicity of, 592t
- Belmont Report, 56, 57t
- bendamustine, 69t  
 genitourinary toxicity of, 617t  
 hepatotoxicity of, 585t  
 as irritant, 366, 367t
- beneficence, 17t
- benzodiazepines, for CINV, 432, 436t
- benzylamine mouthwash, 472, 473t
- beta-blockers, fatigue from, 707t
- BETTER model, for sexuality communication, 649–650
- bevacizumab, 262t  
 cardiotoxicity of, 524t, 536  
 endocrine toxicities from, 690t  
 genitourinary toxicity of, 622t  
 infusion reaction from, 373t  
 pulmonary toxicity of, 565t
- bevacizumab-awwb, 262t
- bexarotene, hepatotoxicity of, 589t
- bicalutamide, 103t
- bile acid malabsorption, 448
- binimetinib, 121t, 193  
 ocular toxicity from, 765t  
 pulmonary toxicity of, 552t
- biologics license application (BLA), 59, 60t
- biomarkers, 38–40, 113, 198, 571. *See also targeted therapies*
- biosafety cabinets, 347–348
- biosimilars, 34–35, 281, 299, 417  
 development of, 62–63
- bispecific mAbs, 272t, 284–285  
 pulmonary toxicity of, 568t
- bispecific T-cell engaging mAbs, 271t–272t
- bisphosphonates  
 genitourinary toxicity of, 623t  
 ocular toxicity of, 763t
- bladder irrigation, for hemorrhagic cystitis, 634–635
- bleomycin, 83t  
 cardiotoxicity of, 502t  
 genitourinary toxicity of, 619t  
 hepatotoxicity of, 588t  
 infusion reaction from, 384t  
 as irritant, 367t  
 pulmonary toxicity of, 545, 548t, 571, 572
- blinatumomab, 271t–272t, 284  
 cardiotoxicity of, 526t  
 infusion reaction from, 373t
- blood–brain barrier, disruption of, 740–741
- blood components, life spans of, 408t, 418
- body fluids, safe handling of, 350–351
- body surface area (BSA), dosing based on, 303, 304f, 306
- bone marrow, 406–408
- bortezomib, 122t, 198  
 cardiotoxicity of, 505t  
 hepatotoxicity of, 592t  
 ocular toxicity from, 765t  
 pulmonary toxicity of, 552t
- bosutinib, 113, 123t  
 cardiotoxicity of, 505t  
 genitourinary toxicity of, 619t  
 hepatotoxicity of, 592t  
 pulmonary toxicity of, 552t
- boundaries, professional, 16
- BRAF inhibitors, 113, 193  
 cutaneous toxicities of, 671–672
- brain tumors, inter-arterial chemotherapy for, 332
- breakthrough CINV, 429, 434–435
- breast cancer, hormone therapy for, 107
- brentuximab vedotin, 214t  
 endocrine toxicities from, 690t  
 genitourinary toxicity of, 622t  
 hepatotoxicity of, 602t  
 infusion reaction from, 373t  
 pulmonary toxicity of, 562t

brexucabtagene autoleucel, 237t–238t, 278  
 cardiotoxicity of, 519t  
 pulmonary toxicity of, 568t  
 brigatinib, 113, 123t–124t  
 cardiotoxicity of, 506t  
 endocrine toxicities from, 687t  
 genitourinary toxicity of, 619t  
 ocular toxicity from, 765t  
 pulmonary toxicity of, 552t  
 Bristol Stool Scale, 451, 477  
 bronchoscopy, 571  
 Brown grading system, for hypersensitivity reactions, 390t  
 Bruton tyrosine kinase (BTK), 193, 448  
 BSA. *See* body surface area  
 BTK inhibitors, 193  
 diarrhea from, 448  
 Budd-Chiari syndrome, 605  
 bulk-forming laxatives, 479, 482t  
 busulfan, 69t  
 cardiotoxicity of, 494t  
 genitourinary toxicity of, 632  
 hepatotoxicity of, 585t  
 ocular toxicity of, 758t  
 pulmonary toxicity of, 545, 546t

## C

cabazitaxel, 93t  
 diarrhea from, 448  
 extravasation of, 363t  
 hepatotoxicity of, 590t  
 infiltration of, 359  
 neurotoxicity of, 737–738  
 cabozantinib, 124t–125t, 198  
 cardiotoxicity of, 506t  
 hepatotoxicity of, 593t  
 cachexia, 442, 442f, 443. *See also* anorexia/cachexia  
 CACI (compounding aseptic containment isolator), 347–348  
 Calvert formula, for carboplatin dosing, 304, 304f  
 camptothecins, 91t–92t, 97–98. *See also* specific agents  
 hepatotoxicity of, 590t  
 pulmonary toxicity of, 549t  
 cancer, defined, 29, 30t, 31  
 cancer cachexia, 442, 442f, 443. *See also* anorexia/cachexia  
 Cancer Care Continuum framework, 31–33  
 cancer clinical trials. *See* clinical trials  
 Cancer Genome Atlas, 38  
 Cancer.Net, 54  
 cancer origins, theories of, 29  
 cancer prevention, 32  
 cancer-related fatigue (CRF). *See* fatigue  
 cancer staging/grading, 33, 34f  
 cancer therapy  
 goals of, 31–32  
 history of, 35t–36t (*See also* cancer treatment modalities)  
 cancer treatment modalities, 33–37, 35t–36t  
 cancer treatment plan, assessment of, 293  
 cannabidiol (CBD) oil, 435  
 cannabinoids  
 for anorexia/cachexia, 444  
 for CINV, 432, 436t–437t  
 fatigue from, 707t  
 capecitabine, 76t  
 cardiotoxicity of, 496t  
 diarrhea from, 448  
 genitourinary toxicity of, 618t  
 hepatotoxicity of, 586t  
 ocular toxicity of, 758t  
 pulmonary toxicity of, 547t  
 capmatinib, 125t, 197  
 hepatotoxicity of, 593t  
 pulmonary toxicity of, 552t  
 carboplatin, 69t–70t, 304, 305, 305f, 306  
 genitourinary toxicity of, 617t  
 infusion reaction from, 384t  
 as irritant, 367t  
 nausea/vomiting from, 434  
 ocular toxicity of, 758t  
 cardiac testing, pretreatment, 302  
 cardiovascular risk factors, 493  
 cardiovascular toxicities, 493. *See also* atrial fibrillation; coronary artery disease; hypertension; left ventricular dysfunction; myocarditis; QT prolongation; venous thromboembolism  
 therapies causing, 494t–527t  
 carfilzomib, 126t, 198  
 cardiotoxicity of, 507t  
 genitourinary toxicity of, 620t  
 hepatotoxicity of, 593t  
 pulmonary toxicity of, 552t  
 carmustine, 90t  
 hepatotoxicity of, 590t  
 as irritant, 367t  
 ocular toxicity of, 760t  
 pulmonary toxicity of, 549t, 550t  
 CD22-directed cytotoxin, 224t–227t  
 CD123-directed cytotoxin, 223t–224t  
 C. difficile colitis, 458, 459, 462, 463  
 CDK inhibitors, 193  
 CD markers, 207, 207t  
 cedazuridine, 78t  
 cell cycle, 67–68, 67f, 657  
 cell cycle-nonspecific drugs, 68, 408  
 cell cycle-specific drugs, 68, 408  
 cell-mediated immunity, 204  
 cellular differentiation, 33. *See also* grading  
 cellular kinetics, 67  
 cellulitis, perirectal, 475–476  
 cemiplimab  
 cardiotoxicity of, 518t  
 endocrine toxicities from, 689t  
 hepatotoxicity of, 600t  
 infusion reaction from, 374t  
 pulmonary toxicity of, 559t  
 cemiplimab-rwlc, 227t  
 Center for Information and Study on Clinical Research Participation, 54  
 central venous access devices, 310, 314–315  
 extravasation from, 361 (*See also* extravasation)  
 cerebellar syndrome, 718t, 730–732  
 cereblon, 282  
 cerebrovascular events, 718t, 732–733  
 ceritinib, 113, 127t, 198  
 cardiotoxicity of, 507t  
 endocrine toxicities from, 687t  
 hepatotoxicity of, 593t  
 ocular toxicity from, 765t  
 pulmonary toxicity of, 552t  
 cetuximab, 251t  
 cardiotoxicity of, 522t

diarrhea from, 448  
 infusion reaction from, 374t  
 ocular toxicity from, 764t  
 pulmonary toxicity of, 562t  
 checkpoint inhibitors, 213, 227t–235t, 276–277, 297  
 cardiotoxicity of, 518t  
 colitis with, 458  
 endocrine toxicities from, 689t, 694–699  
 hepatotoxicity of, 599t–600t  
 as irritants, 366  
 nausea/vomiting with, 431–432  
 neurotoxicity of, 738–739  
 ocular toxicity from, 753, 762t  
 peripheral neuropathy from, 723t  
 pulmonary toxicity of, 544, 557t–559t  
 chemokines, 208  
 chemoprevention, defined, 32, 37  
 chemotherapeutic agents, 68, 69t–96t, 97–98  
 as hazardous drugs, 341–342, 342t (*See also* chemotherapy; specific agents)  
 chemotherapy  
 adherence to, 44–48, 45t, 48f, 309  
 cardiotoxicities of, 493, 494t–527t  
 colitis from, 461t  
 constipation from, 478f  
 cutaneous toxicities of, 657, 669  
 defined, 34, 67  
 diarrhea from, 446–448, 449f, 451, 454–455 (*See also* diarrhea)  
 dosing of, 38  
 endocrine toxicities from, 686t  
 genitourinary toxicities of, 616, 617t–619t, 625, 632, 636–638  
 hepatotoxicity of, 585t–591t  
 high-dose (*See* high-dose chemotherapy)  
 history of, 35t–36t  
 infusion reactions from, 384t–387t  
 nausea/vomiting with, 429, 429f–430f (*See also* nausea and vomiting)  
 neurotoxicity of, 546t–551t, 726–738  
 ocular toxicity of, 758t–761t  
 oral, 44–45, 308–309  
 peripheral neuropathy from, 723t  
 pulmonary toxicity of, 546t–551t  
 resistance to, 42–44  
 response/outcome, 39–44  
 routes of, 308–334  
 second cancer risk with, 778–780  
 Chemotherapy Administration Safety Standards (ASCO/ONS), 16–17, 303  
 chemotherapy errors, 6, 9, 311–312. *See also* verification  
 chemotherapy-induced diarrhea, 446, 447. *See also* diarrhea  
 chemotherapy-induced nausea and vomiting (CINV), 425. *See also* nausea and vomiting  
 chemotherapy-induced neutropenia, 406. *See also* neutropenia  
 chemotherapy trigger zone (CTZ), 425, 426f, 427  
 Child-Pugh classification, of liver disease, 608, 610t  
 Children's Oncology Group, history of, 35t  
 chimeric antigen receptor (CAR) T-cell immunotherapy, 235t–244t, 277–280, 391–392  
 neurotoxicity of, 738  
 chimeric mAbs, 251t–253t, 282, 283f. *See also* monoclonal antibodies

- cardiotoxicity of, 522*t*–523*t*
- ocular toxicity of, 762*t*, 764*t*
- pulmonary toxicity of, 562*t*–564*t*
- chlorambucil, 70*t*
  - hepatotoxicity of, 585*t*
  - ocular toxicity of, 758*t*
  - pulmonary toxicity of, 546*t*
- chlorhexidine, 473*t*
- cholestasis, 604
- chronic cholestasis, 604
- chronic hepatocellular injury, 604
- chronic kidney disease (CKD), 629–631, 630*f*
- chronic lymphocytic leukemia, staging of, 33
- circulating tumor cells, prognosis from, 40
- cisplatin, 70*t*
  - cardiotoxicity of, 494*t*
  - genitourinary toxicity of, 617*t*, 636–637
  - hepatotoxicity of, 585*t*
  - infusion reaction from, 384*t*
  - as irritant, 367*t*
  - neurotoxicity of, 737
  - ocular toxicity of, 758*t*
- cladribine, 77*t*
- clinical benefit response, to chemotherapy, 40
- clinical practicum, 3–4, 792, 793
- clinical research, 53. *See also* clinical trials
- clinical staging, 33
- clinical trials, 53–54
  - barriers to participation, 54, 55*t*
  - enrollment in, 54, 55*t*
  - ethical issues in, 55–57, 57*t*
  - informed consent in, 57, 57*f*
  - phases of, 58, 61*t*
  - protocols for, 54–57, 56*f*
  - regulations/guidance of, 56
  - roles/responsibilities in, 57–58, 59*t*
  - types of, 53, 53*t*
- clofarabine, 77*t*
  - cardiotoxicity of, 501*t*
  - genitourinary toxicity of, 618*t*
  - hepatotoxicity of, 586*t*
- clonal theories, of cancer development, 29
- clonidine, for menopausal symptoms, 647
- closed-system drug-transfer device (CSTD), for compounding HDs, 347–350
- cluster of differentiation (CD) cell expression, 207, 207*t*
- cobimetinib, 128*t*, 193
  - cardiotoxicity of, 507*t*
  - hepatotoxicity of, 593*t*
- Cockcroft-Gault formula, for creatinine clearance, 304, 305*f*
- cognitive behavioral therapy (CBT), for fatigue management, 708–709
- cognitive impairment, 739
  - assessment of, 743–744
  - clinical manifestations of, 743
  - management of, 744
  - pathophysiology of, 739–742, 740*f*
  - patient education on, 744–746
  - risk factors, 742–743
- cognitive rehabilitation, 744
- colectomy, 455, 464
- Coley, William, 35*t*
- Coley toxins, 35*t*
- colitis, 447, 457–459
  - assessment of, 461–462
  - clinical manifestations of, 460, 461*t*
  - differential diagnosis, 461–462
  - immune-mediated, 458–459
  - incidence of, 459
  - management of, 362*f*, 462–464
  - patient education on, 464–465
  - risk factors for, 459–460
- colony-stimulating factors
  - cardiotoxicity of, 519*t*–520*t*
  - for neutropenia, 410–411, 412*t*–414*t*
- combination therapies, 32, 37–38, 98
- Common Terminology Criteria for Adverse Events* (CTCAE), 48–49, 49*t*, 300, 674. *See also specific adverse events*
  - on constipation, 477
  - on cutaneous toxicities, 676*t*–677*t*
  - on diarrhea, 451, 452*f*
  - on febrile neutropenia, 405
  - on hemorrhagic cystitis, 633, 634*f*
  - on hepatic disease, 608, 609*t*
  - on mucositis, 470
- communication
  - during handoffs, 8–9, 23
  - on sexuality issues, 649–650
- comorbidities
  - affecting treatment response, 42
  - assessment of, 294–295
- compassionate use, of drugs/biologics/devices, 63
- competency assessment, 4–5
- complement activation-related pseudo-allergy (CARPA), 393
- complementary and alternative medicine
  - for anorexia/cachexia, 445
  - for cognitive impairment, 744
  - cultural diversity and, 15
  - for fatigue, 709
  - for nausea/vomiting, 435
  - pretreatment review of, 297–298
- complete blood count/differential, pretreatment, 301
- complete response, to chemotherapy, 40
- compounding aseptic containment isolators (CACIs), 347–348
- computed tomography (CT), 444, 461, 543, 570–571, 608
- conditioning therapy, before HSCT, 37
- conduction pathway disorders, 493, 528
- confidentiality, 16
- conflict resolution, 16
- congestive heart failure, 294
- conjugated mAbs, 284, 343, 690*t*, 762*t*. *See also* monoclonal antibodies
- constipation, 476
  - assessment of, 477–479
  - incidence/risk factors, 476–477, 477*t*
  - management of, 479, 480*t*–482*t*
  - pathophysiology of, 476
  - patient education on, 483
  - prevention of, 479–483
- containment primary engineering control (C-PEC) device, for compounding HDs, 347–348
- containment ventilated enclosures (CVEs), 347–348
- continuing education, 4–5
- continuous infusions, 317–318
- control, as treatment intent, 32
- copanlisib, 128*t*–129*t*, 193
  - endocrine toxicities from, 687*t*
  - pulmonary toxicity of, 553*t*
- coronary artery disease, 532–534
- corticosteroids
  - and cancer-related fatigue, 707*t*, 710
  - for CINV, 437*t*
  - for diffuse alveolar hemorrhage, 574
  - for ILD, 572
  - ocular toxicity of, 763*t*
- costs
  - of medication errors, 9
  - of oncology care, 13 (*See also* financial toxicity)
- COVID-19 vaccine, 297
- creatinine clearance, 301, 304, 306
- crizotinib, 113, 129*t*–130*t*, 198
  - cardiotoxicity of, 508*t*
  - genitourinary toxicity of, 620*t*
  - hepatotoxicity of, 593*t*
  - ocular toxicity from, 765*t*
  - pulmonary toxicity of, 553*t*
- CRR/CRS phenotype, 387–391, 387–392. *See also* infusion-related reactions
- cryotherapy (ice chips), 471, 473*t*
- cryptogenic organizing pneumonia, 544
- cultural competency, 14–16, 23
- cultural diversity, 14–16
- curative intent, in cancer treatment, 32, 293
- Curie, Marie and Pierre, 35*t*
- cutaneous toxicities, 657, 658*t*–668*t*
  - assessment of, 673–674
  - management of, 674–675
  - pathophysiology of, 657, 669–673
  - patient education on, 675–677
- cyclin-dependent kinase (CDK) enzymes, 67–68
- cyclin-dependent kinase (CDK) inhibitors, 193
  - diarrhea from, 448
- cyclins, 67–68
- cyclophosphamide, 71*t*
  - cardiotoxicity of, 494*t*–495*t*
  - genitourinary toxicity of, 617*t*, 632
  - hepatotoxicity of, 585*t*
  - mesna dosing with, 635–636
  - ocular toxicity of, 758*t*
  - pulmonary toxicity of, 546*t*, 569
- cyclosporine A, ocular toxicity of, 763*t*
- CYP3A4 inhibitors, drug interactions with, 296
- CYP17 inhibitors, 104*t*, 109
  - drug interactions with, 199
- cystitis. *See* hemorrhagic cystitis
- cytarabine, 77*t*–78*t*, 84*t*–85*t*
  - cardiotoxicity of, 497*t*
  - extravasation of, 363*t*
  - hepatotoxicity of, 586*t*
  - ocular toxicity of, 759*t*
  - pulmonary toxicity of, 547*t*
- cytochrome P450, 104*t*, 109, 199
- cytokine growth factor, 416*t*
- cytokine release syndrome (CRS), 278–279, 293–294
- cytokines, 208, 245*t*–247*t*, 280–282, 407*f*
  - cardiotoxicity of, 520*t*–522*t*
  - endocrine toxicities from, 690*t*, 692
  - genitourinary toxicity of, 622*t*
  - hepatotoxicity of, 601*t*
  - ocular toxicity of, 761*t*
  - pulmonary toxicity of, 560*t*
- cytopenia, 405
  - types of, 406–421
- cytosine arabinoside, pulmonary toxicity of, 569

cytotoxic T cells, 205  
 cytotoxic T-lymphocyte antigen 4 (CTLA-4),  
 207–208, 213  
 CTLA-4 inhibitor, 672  
   cutaneous toxicities of, 672–673  
   endocrine toxicities from, 690*t*, 694  
   hepatotoxicity of, 599*t*  
   pulmonary toxicity of, 557*t*

## D

dabrafenib, 130*t*–131*t*, 193  
   cardiotoxicity of, 508*t*  
   cutaneous toxicities of, 671–672  
   endocrine toxicities from, 687*t*  
   genitourinary toxicity of, 620*t*  
   hepatotoxicity of, 593*t*  
   ocular toxicity from, 765*t*  
 dacarbazine, 71*t*  
   cardiotoxicity of, 495*t*  
   hepatotoxicity of, 585*t*  
   as irritant, 367*t*  
 dacomitinib, 132*t*  
   pulmonary toxicity of, 553*t*  
 dactinomycin, 83*t*  
   extravasation of, 363*t*  
   hepatotoxicity of, 588*t*  
 daratumumab, 255*t*  
   infusion reaction from, 374*t*–375*t*  
   pulmonary toxicity of, 563*t*–564*t*  
 darbepoetin, 412*t*  
 darolutamide, 102*t*  
 dasatinib, 113, 132*t*–133*t*  
   cardiotoxicity of, 508*t*–509*t*  
   hepatotoxicity of, 594*t*  
   pulmonary toxicity of, 553*t*  
 daunorubicin, 84*t*  
   cardiotoxicity of, 498*t*–499*t*  
   extravasation of, 363*t*, 364*t*  
   hepatotoxicity of, 588*t*  
 decitabine, 78*t*  
   endocrine toxicities from, 686*t*  
 deferoxamine mesylate/desferrioxamine, ocular  
   toxicity of, 763*t*  
 degarelix, 105*t*  
 delayed diarrhea, 455  
 delayed-onset CINV, 428, 432–434  
 denosumab, 256*t*  
 depigmentation, 665*t*  
 dermatologic effects. *See* cutaneous toxicities  
 designated priority populations, 15  
 detergent laxatives, 481*t*  
 dexamethasone  
   for anorexia/cachexia, 444  
   for CINV, 432–434, 437*t*  
 dexamethasone mouthwash, 473*t*  
 dextrazoxane, for extravasation management, 365  
 diabetes, 294–295, 697–698  
 diarrhea, 446  
   assessment of, 451–454, 452*f*  
   classifications of, 446–447, 452*f*  
   clinical manifestations of, 451  
   delayed, 455  
   differential diagnosis, 447–448  
   drugs causing, 448–451, 449*f*–450*f*  
   grading of, 446, 446*t*  
   from infection, 448  
   management of, 295, 454–457, 455*t*–456*t*

  pathophysiology of, 446–448  
   patient education on, 457  
   risk factors for, 449*f*–450*f*, 451  
   didactic learning, 3  
   differentiation. *See* grading  
   differentiation syndrome (DS), APL  
     treatment-related, 574–575  
   diffuse alveolar hemorrhage, 573–574  
   dinutuximab  
     cardiotoxicity of, 522*t*  
     infusion reaction from, 376*t*  
   diphenoxylate hydrochloride, for diarrhea, 455*t*  
   disease-free survival, 41  
   disparities, in healthcare, 14  
   distress, 299, 303  
   Distress Thermometer, 299, 798  
   DNA-binding vesicants, extravasation of, 359,  
     364*t*  
   DNA reparability, 44  
   DNA sequence errors, 31  
   DNA sequencing, 38  
   docetaxel, 93*t*–94*t*  
     cardiotoxicity of, 502*t*  
     diarrhea from, 448  
     extravasation of, 359, 360, 363*t*  
     hepatotoxicity of, 591*t*  
     infusion reaction from, 385*t*  
     neurotoxicity of, 737–738  
     ocular toxicity of, 760*t*  
     pulmonary toxicity of, 550*t*, 569  
 documentation  
   errors in, 17  
   of extravasation, 365, 366*f*  
   legal issues of, 17–19  
   of patient education, 24–25  
   of toxicity/adverse events, 48–49, 49*t*  
   of treatment adherence, 47–48, 48*f*  
 dolasetron, for CINV, 439*t*  
 dopamine antagonists, for CINV, 437*t*  
 dose calculations, 303–306, 304*f*, 305*f*  
 dose density, defined, 38  
 dose/drug verification, 7–8  
 dose intensity, defined, 38  
 dose reduction/delay, 38  
 dose rounding, 305–306  
 dosing, of chemotherapy, 38, 303–306, 304*f*, 305*f*.  
   *See also specific chemotherapy routes*  
 dostarlimab-gxly, 227*t*–228*t*  
   pulmonary toxicity of, 559*t*  
 doubling time, of tumor, 67  
 doxepin mouthwash, 473*t*  
 doxorubicin, 85*t*, 86*t*  
   cardiotoxicity of, 498*t*–499*t*  
   extravasation of, 363*t*, 365  
   hepatotoxicity of, 588*t*–589*t*  
   infusion reaction from, 385*t*  
   ocular toxicity of, 759*t*  
 driver variants, 29, 31*t*, 37*t*  
 dronabinol, for CINV, 436*t*  
 drug development, 58–63, 60*t*, 62*t*  
 drug-drug interactions, with targeted therapies,  
   199, 296  
 drug efflux, 44  
 drug errors, 6, 9, 311–312. *See also* verification  
 drug inactivation, 44  
 drug naming, 61–62  
 drug resistance, 42–44  
 drug shortages, 9

  drug target alteration, 44  
   dry skin, 668*t*, 676*t*  
   dual verification, in treatment, 7, 306  
   dual x-ray absorptiometry scans, 444  
   Du Bois and Du Bois formula, for BSA, 303, 304*f*  
   durvalumab, 234*t*–235*t*  
     cardiotoxicity of, 518*t*  
     endocrine toxicities from, 689*t*  
     hepatotoxicity of, 600*t*  
     infusion reaction from, 376*t*  
     pulmonary toxicity of, 558*t*  
   duvelisib, 133*t*, 193  
     diarrhea from, 448  
     hepatotoxicity of, 594*t*  
     pulmonary toxicity of, 553*t*  
   dysentery, 447  
   dyspareunia, 644  
   dystrophy, in nail plate, 659*t*

## E

Eastern Cooperative Oncology Group (ECOG)  
   Performance Status Scale, 42, 43*t*, 299–300, 444  
 echocardiogram, pretreatment, 302  
 ECOG Performance Status Scale, 42, 43*t*  
 ecuzumab, 263*t*  
 education  
   patient (*See* patient education)  
   professional, 3–5  
 educational barriers, 22  
 effector cells, 205  
 effector phase, of immune response, 208  
 EGFR inhibitors, 193–194, 194*f*  
   cutaneous toxicities of, 669–670, 670*f*, 671*f*  
   ocular toxicity from, 753–756, 764*t*  
 electrocardiogram, pretreatment, 302  
 electrolytes  
   pretreatment assessment of, 301  
   repletion of, 454  
 electronic health records, 7  
 elotuzumab, 264*t*  
   cardiotoxicity of, 523*t*  
   endocrine toxicities from, 690*t*  
   hepatotoxicity of, 602*t*  
   infusion reaction from, 376*t*  
   pulmonary toxicity of, 565*t*  
 eltrombopag, 134*t*, 198  
   hepatotoxicity of, 594*t*  
 emergency preparedness, 8  
 emollient laxatives, 479  
 enasidenib, 135*t*, 195  
   genitourinary toxicity of, 620*t*  
   pulmonary toxicity of, 553*t*  
 encephalitis, 728–729  
 encephalopathy, 718*t*–719*t*, 727–730  
 encorafenib, 136*t*, 193  
 endocrine toxicities, 685, 686*t*–691*t*  
 end-of-life decisions, ethics of, 16  
 endometrial cancer, hormone therapy for, 107  
 endoscopic biopsy, for colitis, 461  
 enfortumab vedotin-efv, 215*t*, 284  
   endocrine toxicities from, 690*t*  
   as irritant, 367*t*, 369  
 engineering controls, for compounding HDs,  
   347–349  
 enteral nutrition, 445  
 entrectinib, 137*t*, 197, 198  
 enzalutamide, 103*t*

eosinophils, 408t  
 epidermal growth factor receptors (EGFRs), 193–194, 194f, 207. *See also* EGFR inhibitors  
 epigenetic mechanisms, 31, 194–195  
 epinephrine, for anaphylaxis, 389t  
 epipodophyllotoxins, 92t–93t, 98. *See also specific agents*  
   hepatotoxicity of, 590t  
   ocular toxicity of, 760t  
   pulmonary toxicity of, 550t  
 epirubicin, 86t  
   cardiotoxicity of, 499t  
   extravasation of, 363t  
   hepatotoxicity of, 589t  
 epoetin alfa, 280, 412t  
   cardiotoxicity of, 519t  
 erdafitinib, 138t–139t, 195, 756  
   ocular toxicity from, 765t  
 erectile dysfunction, 643–645, 648–649  
 eribulin, 88t  
   cardiotoxicity of, 504t  
   hepatotoxicity of, 589t  
 erlotinib, 139t  
   genitourinary toxicity of, 620t  
   hepatotoxicity of, 594t  
   ocular toxicity from, 765t  
   pulmonary toxicity of, 554t  
 errors  
   in chemotherapy, 6, 9, 311–312  
   in DNA, 31  
   prevention of, 310–321 (*See also* verification)  
 erythema multiforme, 659t  
 erythema multiforme major, 665t  
 erythrocytes, 418. *See also* red blood cells  
 erythroid maturation agent, 274t–275t  
 erythropoiesis, 417  
 erythropoietin (EPO), 418  
 estradiol, cardiotoxicity of, 495t  
 estramustine, cardiotoxicity of, 495t  
 estrogen receptor antagonists, 104t, 109  
 estrogen therapy, for sexual dysfunction, 648  
 ethambutol, ocular toxicity of, 764t  
 ethical issues  
   in clinical trials, 55–57, 57t  
   in oncology care, 13–16, 17t  
 ethics, defined, 13  
 ethics consultations, 16  
 etoposide, 92t  
   cutaneous toxicities of, 657  
   hepatotoxicity of, 590t  
   infusion reaction from, 385t  
   as irritant, 367t  
   ocular toxicity of, 760t  
   pulmonary toxicity of, 550t  
 European Society for Medical Oncology, on  
   immune-related adverse events, 276  
 evaluation tools, in professional education, 4  
 everolimus, 139t–140t, 197  
   endocrine toxicities from, 687t  
   genitourinary toxicity of, 620t  
   hepatotoxicity of, 594t  
   pulmonary toxicity of, 554t  
 evidence, in professional nursing practice, 3  
 exemestane, 104t  
 exercise  
   with anorexia/cachexia, 445  
   with cognitive impairment, 744  
   with fatigue, 706–708

expanded access, to drugs/biologics/devices, 63  
 exportin 1 (XPO1) inhibitors, 195  
 extravasation, 359, 360, 362t, 801  
   documentation of, 365, 366f, 802  
   follow-up after, 365–366  
   long-term effects of, 361  
   management of, 8, 361–365, 363t–364t  
   risk factors for, 360–361  
   signs/symptoms of, 361, 362t  
 exudative diarrhea, 447  
 eye/face protection, 345. *See also* personal protective equipment  
 EZH2 inhibitors, 195

## F

fam-trastuzumab deruxtecan-nxki, 218t  
   pulmonary toxicity of, 567t  
 fatigue, 703, 704f, 726–727  
   agents associated with, 707t  
   with anemia, 419  
   assessment of, 705–710  
   incidence of, 705  
   management of, 706–710  
   pathophysiology of, 703–705  
   patient education on, 710–711  
 fat malabsorption, 448  
 febrile neutropenia, 405, 408  
   management of, 417–418  
   risk factors for, 408–409, 409f  
 fedratinib, 141t, 196  
   genitourinary toxicity of, 620t  
   hepatotoxicity of, 595t  
 Female Sexual Function Index, 647  
 fertility, alterations in, 650–653  
 fever, 408, 409. *See also* febrile neutropenia  
 FGFR inhibitors, 195  
 fibroblast growth factor receptor (FGFR), 195  
 fidelity, 17t  
 filgrastim, 280, 413t, 417  
   cardiotoxicity of, 519t  
 financial toxicity, 13–14  
   strategies to reduce, 14  
 fissures, of skin, 661t, 675f  
 fixed dosing, 303, 306  
 flare reaction, from infusion, 359, 361, 370  
 floxuridine, hepatotoxicity of, 587t  
 FLT3 inhibitors, 195–196  
 fludarabine, 79t  
   genitourinary toxicity of, 618t  
   ocular toxicity of, 759t  
   pulmonary toxicity of, 547t  
 fluid resuscitation, during diarrhea, 454  
 flutamide, 103t  
 FMS-like tyrosine kinase 3 (FLT3) inhibitors, 195–196  
 focal neurologic deficits, 730, 731t  
 Food and Drug Administration (FDA)  
   in drug development process, 58–63, 60t  
   Safety and Innovation Act (2012), 9  
 fosaprepitant, for CINV, 439t  
 fosnetupitant, for CINV, 441t  
 Foundation for the Accreditation of Cellular  
   Therapy (FACT), safety monitoring by, 0  
 Friends of Cancer Research, 54  
 fulvestrant, 104t, 109  
 Functional Assessment of Anorexia-Cachexia  
   Therapy, 444

## G

gabapentin, for sexual dysfunction, 647  
 Gastrointestinal Symptom Rating Scale, 451  
 gastrointestinal toxicities. *See* anorexia/cachexia; colitis; constipation; diarrhea; mucositis; nausea and vomiting; pancreatitis; perirectal cellulitis  
 gefitinib  
   hepatotoxicity of, 595t  
   ocular toxicity from, 765t  
   pulmonary toxicity of, 554t  
 gemcitabine, 80t  
   cardiotoxicity of, 501t  
   genitourinary toxicity of, 618t  
   hepatotoxicity of, 587t  
   as irritant, 368t  
   ocular toxicity of, 759t  
   pulmonary toxicity of, 547t, 569  
 gemtuzumab ozogamicin, 221t  
   hepatotoxicity of, 602t  
   infusion reaction from, 376t  
 gender identity, 299  
 generic drugs, 61–62  
 gene therapies, defined, 34–36  
*Genetics/Genomics Nursing: Scope and Standards of Practice*, 17  
 genitourinary toxicities, 615, 617t–623t. *See also* acute kidney injury; chronic kidney disease; hemorrhagic cystitis; SIADH; tumor lysis syndrome  
 germline cancers, 31  
 gilteritinib, 143t, 196  
   genitourinary toxicity of, 620t  
   pulmonary toxicity of, 554t  
 glasdegib, 144t–145t, 196  
   genitourinary toxicity of, 620t  
 gloves/gowns, 344–345. *See also* personal protective equipment  
 glucocorticoids, endocrine toxicities from, 691t, 693–694, 695f  
 glutamine, for oral mucositis, 473t  
 goserelin, 105t  
 grading  
   of adverse events, 48–49, 49t, 279  
   of tumors, 33  
 graft-versus-host disease (GVHD), genitourinary  
   effects of, 633  
 granisetron, for CINV, 440t  
 granulocyte-colony-stimulating factor (G-CSF),  
   for neutropenia, 411  
 granulocyte macrophage-colony-stimulating factor (GM-CSF), for neutropenia, 411  
 granulocytes, 205  
 granulomas, 605  
 growth factors, for neutropenia, 412t–416t  
 growth fraction, of tumor, 67

## H

hair loss. *See* alopecia  
 haloperidol, for CINV, 437t  
 hand-foot skin reaction, 671  
 hand-foot syndrome, 657, 662t, 669  
 handoffs, communication during, 8–9, 23  
 hazardous drugs (HDs). *See also* personal protective equipment; safe handling  
   administration of, 349–350  
   chemotherapy drugs as, 341–342, 342t



- compounding of, 347–349
  - defined, 341
  - disposal of, 351
  - in home settings, 346f–347f
  - policies/procedures on, 5–6, 353–354
  - post-exposure procedures, 350–353, 352f
  - storage/labeling of, 345–347, 346f–347f
  - transportation of, 349
  - HDAC inhibitors, 194–195
  - headache, 719t, 735
  - healthcare disparities, 14
  - health literacy, 21, 22. *See also* patient education
  - heart failure, 534–537
  - heated intraperitoneal chemotherapy (HIPEC), 320–321
  - Hedgehog pathway inhibitors, 196
  - height/weight, pretreatment review of, 300
  - helper T cells, 205
  - hematopoiesis, 405–406, 407f
  - hematopoietic growth factors, 280–281, 412t–414t
  - hematopoietic stem cell mobilizers, 414t–415t
  - hematopoietic stem cells (HSCs), 405–406, 407f
  - hematopoietic stem cell transplantation (HSCT), 35–37
    - alveolar hemorrhage with, 573
    - genitourinary toxicities with, 623, 632
    - long-term/late effects of, 785
  - hemophagocytic lymphohistiocytosis/macrophage-activation syndrome (HLH/MAS), 279
  - hemorrhagic cystitis, 631–636
  - hemorrhagic pneumonitis, 544
  - hepatic arterial infusions, 331
  - hepatic sinusoidal obstruction syndrome (SOS), 605–606, 607t
  - hepatic toxicities, 583, 604–606
    - assessment of, 606
    - clinical manifestations of, 584, 604
    - management of, 608–610, 609t, 610t
    - pathophysiology of, 583–584
    - patient education on, 609–610
    - risk factors for, 584
    - treatments causing, 585–603t
  - hepatic venous outflow obstruction, 605
  - hepatitis B testing, 301–302
  - hepatocellular injury, 604
  - HER2 inhibitors, 196
  - hereditary cancers, 31
  - high-dose chemotherapy
    - with cyclophosphamide, 494t–495t
    - defined, 35–37
    - with methotrexate, 296
  - hirsutism, 660t
  - HLH/MAS (hemophagocytic lymphohistiocytosis/macrophage-activation syndrome), 279
  - Hodgkin lymphoma, staging of, 33
  - honey, for oral mucositis, 473t
  - hormone replacement therapy, for sexual dysfunction, 648
  - hormone therapy
    - agents for, 102t–106t (*See also specific agents*)
    - cancers treated with, 101–107
    - categories of, 107–110
    - defined, 34, 101
    - endocrine toxicities from, 691t
    - fatigue from, 707t
    - hepatotoxicity of, 603t
    - ocular toxicity of, 761t
  - human epidermal growth factor receptor (HER), 196
  - Human Genome Project, 36t
  - humanized mAbs, 261t–270t, 282, 283f. *See also* monoclonal antibodies
    - cardiotoxicity of, 524t–526t
    - genitourinary toxicity of, 622t
    - hepatotoxicity of, 602t–603t
    - ocular toxicity of, 762t–763t
    - pulmonary toxicity of, 565t–567t
  - human mAbs, 255t–260t, 282–283, 283f. *See also* monoclonal antibodies
    - cardiotoxicity of, 523t
    - endocrine toxicities from, 690t
    - hepatotoxicity of, 601t–602t
    - ocular toxicity of, 762t
    - pulmonary toxicity of, 565t
  - humoral immunity, 204
  - hyaluronidase, 253t–256t, 267t–268t, 270t
    - cardiotoxicity of, 525t
    - for extravasation management, 365
    - infusion reaction from, 375t, 381t
    - pulmonary toxicity of, 563t–564t, 566t, 567t
  - hydration, for TLS management, 629
  - hydroxyurea, 88t
    - genitourinary toxicity of, 618t
    - hepatotoxicity of, 590t
  - hyperglycemia, 694, 695f, 697
  - hyperpigmentation, 660t, 675f
  - hypersensitivity pneumonitis, 544, 569–570
  - hypersensitivity reactions, 293–294, 388t–389t, 390t. *See also* anaphylaxis; infusion-related reactions
  - hypertension, 530–532
  - hyperthyroidism/hypothyroidism, 691–696
  - hypertrichosis, 660t
  - hypocalcemia, 454
  - hypokalemia, 454
  - hypomagnesemia, 454
  - hypophosphataemia, 454
  - hypophysis, 696–697, 719t
  - hypoxia, 419–420, 572
- I**
- ibrutinib, 145t, 193
    - cardiotoxicity of, 509t
  - idarubicin, 86t
    - cardiotoxicity of, 499t
    - extravasation of, 363t
    - hepatotoxicity of, 589t
  - idecabtagene vicleucel, 241t–242t, 278
    - cardiotoxicity of, 519t
    - pulmonary toxicity of, 568t
  - idelalisib, 146t, 193
    - diarrhea from, 448
    - hepatotoxicity of, 595t
    - pulmonary toxicity of, 554t
  - IDH inhibitors, 195
  - ifosfamide, 71t–72t
    - cardiotoxicity of, 495t
    - genitourinary toxicity of, 617t
    - hepatotoxicity of, 585t
    - as irritant, 368t
    - ocular toxicity of, 758t
    - pulmonary toxicity of, 546t
  - imatinib mesylate, 113, 147t
    - cardiotoxicity of, 509t
  - endocrine toxicities from, 687t
  - genitourinary toxicity of, 620t
  - hepatotoxicity of, 595t
  - ocular toxicity from, 766t
  - pulmonary toxicity of, 554t
  - immune checkpoint inhibitors, 213, 227t–235t, 276–277, 297
    - cardiotoxicity of, 518t
    - endocrine toxicities from, 689t, 694–699
    - hepatotoxicity of, 599t–600t
    - as irritants, 366
    - nausea/vomiting with, 431–432
    - neurotoxicity of, 738–739
    - ocular toxicity from, 753, 762t
    - peripheral neuropathy from, 723t
    - pulmonary toxicity of, 544, 557t–559t
  - immune checkpoints, 207, 213
  - immune effector cell-associated neurotoxicity syndrome (ICANS), 279
  - immune-related adverse events (irAEs), 276–277, 278. *See also* immunotherapy
  - immune responses
    - phases of, 208
    - types of, 203–205, 204f, 205t
  - immune surveillance, 208
  - immune system, 203, 203f
    - cells of, 205–206, 206f
    - organs of, 204
    - pathophysiology of, 213, 276–277
    - proteins/receptors of, 206–208
  - immunizations, pretreatment review of, 297
  - immunoeediting, 209
  - immunomodulators, 248t–250t, 282
    - cardiotoxicity of, 526t–527t
    - endocrine toxicities from, 690t
    - hepatotoxicity of, 601t
    - peripheral neuropathy from, 723t
    - pulmonary toxicity of, 561t
  - immunosuppression, defined, 37
  - immunotherapy
    - agents for, 214t–275t (*See also specific agents*)
    - cardiotoxicity of, 517t–528t
    - colitis from, 458–460, 461t, 463–464
    - constipation from, 478f
    - cutaneous toxicities from, 672–673, 673f
    - defined, 34–39, 203, 213
    - diarrhea from, 447, 448–451, 450f, 451
    - drug interactions with, 297
    - endocrine toxicities from, 689t–690t
    - genitourinary toxicity of, 622t, 623, 625
    - hazardous drugs in, 343
    - hepatotoxicity of, 599t–603t, 608–609
    - infusion reactions from, 372t–383t
    - as irritants, 366
    - modalities of, 213–287
    - nausea/vomiting with, 429–430, 429f–430f (*See also* nausea and vomiting)
    - neurotoxicity of, 738–739
    - ocular toxicity of, 761t–763t
    - patient education on, 277, 280–282, 287, 287f
    - pulmonary toxicity of, 557t–569t
    - response criteria for, 40–41
    - second cancer risk with, 780
    - sexual dysfunction from, 645
  - implanted intra-arterial pumps, 333–334
  - implicit bias, 15
  - IM routes, for chemotherapy, 309–310
  - IND. *See* Investigational New Drug application



independent dual verification, in treatment, 7, 306

infection

- colitis from, 458, 459, 462, 463
- cutaneous effects of, 675
- diarrhea from, 448, 454
- hemorrhagic cystitis from, 633
- with neutropenia, 409
- pharmacologic management of, 295
- prevention of, 411–417, 421
- pulmonary, 573
- skin protection against, 411

infertility, 650–653

infigratinib, 148*t*

- genitourinary toxicity of, 620*t*

infiltrations, of IV drugs, 359, 366–370, 367*t*–368*t*

inflammation theory, of cancer development, 29

inflammatory diarrhea, 447

influenzers, on professional nursing practice, 3

influenza vaccine, 297

informed consent

- in clinical trials, 57, 57*f*
- elements of, 18–19, 797
- legal issues of, 18–19
- by minors, 19
- pretreatment review of, 299

Infusion Nurses Society, 17, 310

infusion pumps, 311

infusion-related reactions, 293–294, 359, 370, 371*f*. *See also* anaphylaxis

- management of, 387–397, 388*t*–389*t*, 394*f*–395*f*
- patient education on, 397
- risk factors for, 390–392

*Infusion Therapy Standards of Practice*, 17, 310

innate immunity, 203, 204*f*, 205*t*, 206*f*

inotuzumab ozogamicin, 222*t*

- hepatotoxicity of, 602*t*
- infusion reaction from, 377*t*

institutional review boards (IRBs), 56–57

interferons (IFNs), 245*t*–246*t*, 281

interleukins (ILs), 246*t*–247*t*, 281, 421

- cardiotoxicity of, 521*t*–522*t*
- endocrine toxicities from, 692
- genitourinary toxicity of, 622*t*
- hepatotoxicity of, 601*t*
- ocular toxicity of, 761*t*
- pulmonary toxicity of, 560*t*

interleukins (ILs), 246*t*–247*t*, 281, 421

- cardiotoxicity of, 521*t*–522*t*
- endocrine toxicities from, 692
- genitourinary toxicity of, 622*t*
- hepatotoxicity of, 601*t*
- ocular toxicity of, 761*t*
- pulmonary toxicity of, 560*t*, 569

intermittent/minibag infusion, 311, 316–317

International Index of Erectile Function, 648

International Staging System, 33

interstitial lung disease (ILD), 543

- assessment of, 570–571
- clinical manifestations of, 570
- incidence of, 544–545
- management of, 571–573
- pathophysiology of, 543–544
- risk factors for, 545, 569–570

intra-arterial chemotherapy, 331–334

intra-arterial ports, 333

intra-arterial pumps, implanted, 333–334

intracranial hemorrhage, 718*t*, 732–733

intramuscular (IM) routes, for chemotherapy, 309–310

intraperitoneal chemotherapy, 318–321

intrapleural chemotherapy, 334

intrathecal chemotherapy, 321–324

intravenous routes, for chemotherapy, 310–318

intraventricular chemotherapy, 324–326

intravesical (bladder) chemotherapy, 326–328

intrinsic drug resistance, 44

Investigational New Drug (IND) application, 58, 60*t*, 63

ipilimumab

- cardiotoxicity of, 518*t*
- colitis from, 459
- endocrine toxicities from, 690*t*
- hepatotoxicity of, 599*t*
- pulmonary toxicity of, 557*t*

iRECIST criteria, for tumor response, 40–41

irinotecan, 92*t*

- diarrhea from, 448, 454–455
- hepatotoxicity of, 590*t*
- as irritant, 368*t*, 369

irinotecan-induced cholinergic syndrome, 393

irritation, from infusion, 359, 361, 366–370, 367*t*–368*t*

isatuximab-irfc, 252*t*

- infusion reaction from, 377*t*
- pulmonary toxicity of, 562*t*

ischemic stroke, 718*t*, 732–733

isolated limb perfusion, 331–332

itching, 664*t*

ivosidenib, 150*t*, 195

- genitourinary toxicity of, 621*t*
- pulmonary toxicity of, 554*t*

IV piggyback technique, 311, 316–317

IV push method, 315–316

IV routes, for chemotherapy, 310–318

ixabepilone, 89*t*

- hepatotoxicity of, 590*t*
- infusion reaction from, 386*t*

ixazomib, 149*t*, 198

- genitourinary toxicity of, 621*t*
- hepatotoxicity of, 595*t*

## J

JAK/STAT signaling pathway, 196

Janus kinase (JAK) inhibitors, 196

The Joint Commission, ethics consultations by, 16

justice, 17*t*

## K

Karnofsky Performance Status Scale, 42, 43*t*, 300, 444

ketoconazole, 104*t*, 109

kinase inhibitor, 416*t*

King, Mary-Claire, 36*t*

Kirsten rat sarcoma viral oncogene homolog (KRAS) inhibitors, 196

## L

labeling, of hazardous drugs, 345–347

laboratory tests

- for anemia, 420*t*
- for anorexia/cachexia, 444
- for colitis, 460–461
- for liver disease, 608
- for pancreatitis, 466
- pretreatment assessment of, 300–302

language barriers, to patient education, 22, 23

lanreotide, endocrine toxicities from, 691*t*

Lansky Play-Performance Scale for Pediatric Patients, 42, 43*t*

lapatinib, 151*t*, 196

- cardiotoxicity of, 510*t*
- hepatotoxicity of, 596*t*
- pulmonary toxicity of, 555*t*

larotrectinib, 152*t*, 197

L-asparaginase

- hepatotoxicity of, 589*t*
- pancreatitis with, 466

late effects. *See* long-term/late effects

laxatives, for constipation management, 479, 480*t*–482*t*

learning needs assessments, 22, 23

left ventricular dysfunction, 534–537

legal issues, in oncology care, 16–19

lenalidomide, 248*t*–249*t*

- cardiotoxicity of, 526*t*
- endocrine toxicities from, 690*t*
- genitourinary toxicity of, 622*t*
- hepatotoxicity of, 601*t*
- pulmonary toxicity of, 561*t*

lenvatinib, 153*t*, 198

- cardiotoxicity of, 510*t*
- endocrine toxicities from, 687*t*
- genitourinary toxicity of, 621*t*
- hepatotoxicity of, 596*t*

letrozole, 104*t*

leukoencephalopathy, 720*t*, 724, 741

leuprolide, 105*t*

- endocrine toxicities from, 691*t*

Lexicomp, 296

LHRH agonists/antagonists, 105*t*, 107–108. *See also specific agents*

libido decrease, 644

life support, certification in, 8

linens, safe handling of, 351

lisocabtagene maraleucel, 239*t*–240*t*, 277–278

- cardiotoxicity of, 519*t*
- pulmonary toxicity of, 569*t*

liver biopsy, 608

liver disease, 295. *See also* hepatic toxicities

liver function tests, 301, 608

lomustine, 91*t*

- hepatotoxicity of, 590*t*
- pulmonary toxicity of, 545, 550*t*

loncastuximab tesirine-lpyl, 219*t*

- as irritant, 368*t*, 369
- pulmonary toxicity of, 568*t*

long-term/late effects

- of breast cancer, 781
- of cervical cancer, 781–782
- of Hodgkin lymphoma, 782–783
- of lung cancer, 783
- of non-Hodgkin lymphoma, 783
- patient education on, 786
- of prostate cancer, 783
- screening of, 785–786
- in survivorship, 775–786, 776*t*–777*t*
- of testicular cancer, 783–784

loperamide, for diarrhea, 454, 455*t*, 472

lorazepam, for CINV, 433–434, 436*t*

lorlatinib, 113, 154*t*, 198

- endocrine toxicities from, 688*t*
- genitourinary toxicity of, 621*t*
- hepatotoxicity of, 596*t*

ocular toxicity from, 765*t*  
 pulmonary toxicity of, 555*t*  
 low-level laser therapy, for mucositis, 471, 473*t*  
 lubricant laxatives, 479, 481*t*  
 lumbar puncture, 321–324  
 lung biopsy, 571  
 lurbinectedin, 72*t*  
   extravasation of, 363*t*  
   hepatotoxicity of, 586*t*  
 luspatercept-aamt, 274*t*–275*t*  
 luteinizing hormone-releasing hormone (LHRH), 107  
 lymphocytes, 205–206, 208

## M

macrophages, 408*t*  
 magnetic resonance imaging (MRI), 444  
 Malnutrition Screening Tool (MST), 444  
 Malnutrition Universal Screening Tool (MUST), 444  
 mammalian target of rapamycin (mTOR) kinase inhibitors, 196–197  
   diarrhea from, 448  
   endocrine toxicities from, 685, 691  
   pulmonary toxicity of, 569  
 mannitol, ocular toxicity of, 764*t*  
 MAPK signaling pathway, 193  
 margetuximab-cmkb, 254*t*  
 MD Anderson Symptom Inventory, 49  
 mechlorethamine, 72*t*  
   ocular toxicity of, 758*t*  
 medical cannabis, 435  
 medical records, 17. *See also* documentation  
 medication errors, 6, 9  
   factors/risk of, 6–9  
   prevention of, 311–312 (*See also* verification)  
 medications, pretreatment review of, 295–297  
 megestrol acetate, for anorexia/cachexia, 444  
 MEK inhibitors, 113, 193  
   diarrhea from, 448  
 melphalan, 72*t*–73*t*  
   cardiotoxicity of, 496*t*  
   genitourinary toxicity of, 617*t*  
   hepatotoxicity of, 586*t*  
   as irritant, 368*t*, 369  
   pulmonary toxicity of, 546*t*  
 memory B cells, 206  
 memory T cells, 205  
 meningitis, 718*t*, 733  
 Menopausal Sexual Interest Questionnaire, 647  
 mesenchymal-epithelial transition factor (MET) inhibitors, 197  
 mesna, for hemorrhagic cystitis, 635–636  
 methotrexate, 80*t*–81*t*, 296  
   genitourinary toxicity of, 618*t*, 637–638  
   hepatotoxicity of, 587*t*  
   ocular toxicity of, 759*t*  
   pulmonary toxicity of, 547*t*, 569  
 methylnaltrexone, for constipation, 480*t*  
 MET inhibitors, 197  
 metoclopramide  
   for anorexia/cachexia, 444  
   for CINV, 434, 438*t*  
 microenvironment changes  
   cancer development from, 31, 208  
   treatment response and, 44  
 midline catheters, 310  
 midostaurin, 155*t*, 196  
   endocrine toxicities from, 688*t*  
   pulmonary toxicity of, 555*t*  
 minibag infusion, 311, 316–317  
 minors, informed consent by, 19  
 mirtazapine, for anorexia/cachexia, 444  
 mitogen-activated extracellular signal regulated (MEK) inhibitors, 113, 193  
   diarrhea from, 448  
 mitogen-activated protein kinase (MAPK) signaling pathway, 193  
 mitomycin C, 84*t*  
   extravasation of, 363*t*  
   genitourinary toxicity of, 619*t*  
   hepatotoxicity of, 588*t*  
   ocular toxicity of, 760*t*  
   pulmonary toxicity of, 545, 548*t*  
 mitotane, 89*t*, 102*t*, 110  
   endocrine toxicities from, 686*t*  
   ocular toxicity of, 760*t*  
 mitoxantrone, 87*t*  
   cardiotoxicity of, 500*t*  
   extravasation of, 363*t*  
   hepatotoxicity of, 588*t*  
   ocular toxicity of, 760*t*  
   pulmonary toxicity of, 548*t*  
 mobocertinib, 155*t*–156*t*  
   cardiotoxicity of, 510*t*  
   pulmonary toxicity of, 555*t*  
 mogamulizumab-kpkc, 264*t*  
   infusion reaction from, 378*t*  
 monoclonal antibodies (mAbs), 207, 251*t*–272*t*, 282–286, 283*f*  
   cardiotoxicity of, 522*t*–526*t*  
   colitis with, 458, 459  
   endocrine toxicities from, 690*t*  
   febrile neutropenia with, 408  
   genitourinary toxicity of, 622*t*  
   as hazardous drugs, 343  
   hepatotoxicity of, 601*t*–603*t*  
   nausea/vomiting with, 429–430 (*See also* nausea and vomiting)  
   ocular toxicity of, 762*t*, 764*t*  
   patient education on, 285  
   pulmonary toxicity of, 562*t*–567*t*  
   spill management of, 353  
   toxicities of, 285, 293–294  
 monocytes, 408*t*  
 Mosteller formula, for BSA, 303–304, 304*f*  
 mouth rinses, for mucositis, 472, 473*t*–474*t*  
 moxetumomab pasudotox-tdfk, 224*t*–227*t*  
   infusion reaction from, 378*t*  
 mTOR kinase inhibitors, 196–197  
   diarrhea from, 448  
   endocrine toxicities from, 685, 691  
   pulmonary toxicity of, 569  
 mucositis, 467  
   assessment of, 469–470  
   clinical manifestations of, 469  
   incidence of, 468  
   management of, 471–472, 473*t*–474*t*  
   pain management with, 472, 473*t*–474*t*  
   pathophysiology of, 467–468  
   patient education on, 472–474  
   prevention of, 471–472  
   risk factors for, 468–469  
 multidrug resistance, 44  
 Multinational Association of Supportive Care in Cancer (MASCC)

on CINV management, 432–434  
 on cutaneous toxicities, 671*f*, 674  
 multiple kinase agents, 198  
 multiple myeloma, staging of, 33  
 murine mAbs, 282, 283*f*. *See also* monoclonal antibodies  
   cardiotoxicity of, 526*t*  
   muscle relaxants, fatigue from, 707*t*  
   mutations, 29–31. *See also* variants  
   myeloablative therapy, defined, 37  
   myeloid cells, 205  
   myelopathy, 719*t*, 734  
   myelosuppression, 405–406. *See also* anemia; cytopenia; thrombocytopenia  
 myocardial ischemia, 532–533  
 myocarditis, 537–539

## N

nabilone, for CINV, 437*t*  
 nab-paclitaxel, 95*t*  
   neurotoxicity of, 737–738  
 nadirs, of blood cells, 405, 408, 418  
 nail changes, 661*t*  
 naldemedine, for constipation, 480*t*  
 naming conventions, for drugs, 61–62  
 National Action Plan to Improve Health Literacy, 21  
 National Cancer Act (1937), 35*t*  
 National Cancer Act (1971), 35*t*  
 National Cancer Institute, 24, 35*t*, 36*t*  
   Cancer Information Service, 54  
   Cancer Therapy Evaluation Program (CTEP), 48, 300  
 National Community Oncology Dispensing Association, on treatment adherence, 46, 47  
 National Comprehensive Cancer Network (NCCN)  
   on distress screening, 299, 303, 798  
   drug order templates, 7, 293, 794  
   on fatigue assessment, 706  
   on febrile neutropenia, 405  
   on immune-related adverse events, 276  
   on scalp cooling, 680  
 National Institute for Occupational Safety and Health (NIOSH), 341–343  
 National Research Act (1974), 55–56  
 natural killer (NK) cells, 206, 408*t*  
 nausea and vomiting, 425  
   assessment of, 429–430, 429*f*–430*f*, 431*f*, 432*t*  
   classifications of, 428–429  
   complications of, 430–431  
   dietary interventions for, 435  
   management of, 431–435  
   nonpharmacologic management of, 435  
   pathophysiology of, 425–428, 426*f*, 427*f*  
   patient education on, 435–442  
   pharmacologic management of, 295–296, 431–432, 436*t*–441*t*  
   risk factors for, 428–429  
 naxitamab-gqgk, 265*t*  
 necitumumab, 257*t*  
   infusion reaction from, 378*t*  
 nelarabine, 81*t*  
   genitourinary toxicity of, 618*t*  
   hepatotoxicity of, 587*t*  
 neoadjuvant therapy, defined, 37  
 neratinib, 156*t*, 196

netupitant, for CINV, 441t  
 neurokinin-1 (NK<sub>1</sub>) antagonists, for CINV, 432, 433, 441t  
 neurotoxicity, 717  
   chemotherapy-induced, 546t–551t, 726–738  
   radiation-induced, 717–721  
   risk factors/prophylaxis for, 739  
 neurotrophin receptor tyrosine kinase (NTRK) inhibitors, 197  
 neutropenia, 405–418, 406t. *See also* febrile neutropenia  
   management of, 410–418, 412–416t  
   patient education on, 411  
   prevention of, 411–417  
   risk factors for, 408–409, 409f  
 neutropenic diets, 410  
 neutropenic enterocolitis, 448, 457–460, 463. *See also* colitis  
 neutrophils, 406–408, 408t  
 new drug application (NDA), 59, 60t  
 nilotinib, 113, 157t  
   cardiotoxicity of, 511t  
   hepatotoxicity of, 596t  
   ocular toxicity from, 766t  
 nilutamide, 103t  
 NIOSH List of Antineoplastic and Other Hazardous Drugs, 342–343  
 niraparib, 158t, 197  
   cardiotoxicity of, 511t  
 nitrogen mustard, 35t, 72t, 495t  
 nitrosoureas, 90t–91t, 97. *See also specific agents*  
   endocrine toxicities from, 686t  
   hepatotoxicity of, 590t  
   ocular toxicity of, 760t  
   pulmonary toxicity of, 549t–550t  
 nivolumab, 228t–229t  
   colitis from, 458  
   endocrine toxicities from, 689t  
   hepatotoxicity of, 599t  
   infusion reaction from, 379t  
   pulmonary toxicity of, 559t  
 NK<sub>1</sub> (neurokinin-1) antagonists, for CINV, 432, 433, 441t  
 NK cells, 206, 408t  
 non-DNA-binding vesicants, extravasation of, 359, 364t  
 nonmaleficence, 17t  
 nonmyeloablative therapy, defined, 37  
 nonsteroidal anti-inflammatory drugs (NSAIDs), drug interactions with, 296–297  
 NTRK inhibitors, 197  
 Nuremberg trials, 55–56  
 nurse practice acts, 16  
 nursing practice, professional, 3  
 Nutrition Risk Screening 2002, 444

## O

obesity, dosing calculations and, 304–305, 305f  
 obinutuzumab, 266t  
   hepatotoxicity of, 603t  
   infusion reaction from, 379t  
   pulmonary toxicity of, 566t  
 objective response rate, 41  
 objective tumor response, to chemotherapy, 39–40  
 occupational exposure  
   cancer development from, 31

  procedures following, 351–353, 352f  
   professional, 341, 350 (*See also* safe handling)  
 octreotide  
   for diarrhea, 454, 456t, 474t  
   endocrine toxicities from, 691t  
 ocular toxicities, 753, 754t–755t, 756t, 758t–766t  
   assessment of, 757, 767  
   clinical manifestations of, 757  
   incidence/risk factors for, 757  
   management of, 767  
   pathophysiology of, 753–757  
   patient education on, 767  
 ofatumumab, 258t  
   hepatotoxicity of, 603t  
   infusion reaction from, 379t  
   pulmonary toxicity of, 564t  
 Office of Cancer Complementary and Alternative Medicine, 297–298  
 Office of Disease Prevention and Health Promotion, on health literacy, 21  
 off-label use, of drugs, 63  
 olanzapine  
   for anorexia/cachexia, 444  
   for CINV, 432, 433, 435, 436t  
 olaparib, 158t–159t, 197  
   pulmonary toxicity of, 555t  
 olaratumab, infusion reaction from, 380t  
 older adults  
   oral mucositis in, 469  
   pretreatment assessment of, 298  
 omacetaxine, 89t  
   endocrine toxicities from, 686t  
 Ommaya reservoir, 324–326  
 Oncology Nursing Society (ONS)  
   Access Device Standards of Practice, 17, 310  
   on patient-reported outcome assessment, 300  
   safety standards of, 3, 16–17  
   Scope and Standards of Oncology Nursing Practice, 16  
   on skin/hair toxicities, 669, 671, 678, 680  
 oncolytic viral therapy, 273t–274t, 286–287  
   safe handling of, 286–287  
 oncogenic genes, 29, 31t, 37t  
 ondansetron, for CINV, 441t  
 onycholysis, 661t  
 oocyte/embryo cryopreservation, 651  
 opioids  
   constipation from, 476–477, 477t, 479, 483  
   fatigue from, 707t  
 oprelvekin, 415t  
   cardiotoxicity of, 522t  
 Optimal Resources for Cancer Care (ACOS CoC), 17  
 Oral Assessment Guide, 470  
 oral care, during mucositis, 471, 472–473  
 oral chemotherapy, 44–46, 308–309  
 Oral Chemotherapy Education sheets, 46  
 oral cryotherapy, 471, 473t  
 oral mucositis  
   assessment of, 469–470  
   clinical manifestations of, 469  
   incidence of, 468  
   management of, 471–472, 473t–474t  
   pain management with, 472, 473t–474t  
   patient education on, 472–474  
   prevention of, 471–472  
 Oral Toxicity Scale (World Health Organization), 470

ordering errors, 6, 7  
 organizational health literacy, 21  
 osimertinib, 160t  
   cardiotoxicity of, 511t  
   pulmonary toxicity of, 555t  
 osmotic diarrhea, 446–447  
 osmotic laxatives, 479, 480t  
 ototoxicity, 720t  
 ovarian cancer, hormone therapy for, 107  
 overweight patients, dosing calculations for, 304–305, 305f  
 oxaliplatin, 73t  
   genitourinary toxicity of, 618t  
   hepatotoxicity of, 586t  
   infusion reaction from, 386t  
   as irritant, 368t, 369  
   neurotoxicity of, 737  
   ocular toxicity of, 758t  
   pulmonary toxicity of, 546t

## P

P13K inhibitors, 193, 459  
 paclitaxel, 94t  
   cardiotoxicity of, 503t  
   diarrhea from, 448  
   extravasation of, 359–360, 363t  
   hepatotoxicity of, 591t  
   infusion reaction from, 386t, 393  
   neurotoxicity of, 737–738  
   ocular toxicity of, 760t  
   pulmonary toxicity of, 551t, 569  
 palbociclib, 161t, 193  
   pulmonary toxicity of, 555t  
 palifermin, 416t, 471, 473t  
 palliation, as treatment intent, 32  
 palmar-plantar erythrodysesthesia, 657, 662t, 669  
 palonosetron, for CINV, 433, 441t  
 pamidronate, genitourinary toxicity of, 623t  
 PAMORAs, for constipation management, 479, 480t  
 pancreatitis, 465  
   assessment of, 466  
   clinical manifestations of, 466  
   incidence/risk factors, 465–466  
   management of, 466–467  
 pancytopenia, 405  
 panitumumab, 259t  
   diarrhea from, 448  
   infusion reaction from, 380t  
   pulmonary toxicity of, 565t  
 panobinostat, 161t–162t, 195  
   cardiotoxicity of, 512t  
   hepatotoxicity of, 596t  
 papulopustular rash, 658t, 669, 670f, 676t–677t  
 paraneoplastic diarrhea, 447  
 parenteral nutrition, 445  
 paronychia, 663t, 674f, 676t  
 PARP inhibitors, 197  
   diarrhea from, 448  
 passenger variants, 29–31  
 pathologic staging, 33  
 patient education, 21  
   barriers to, 22–23  
   documentation of, 24–25  
   methods of, 23–24  
   on oral chemotherapy, 46  
   outcomes of, 21–22

- Patient Education Materials Assessment Tool (PEMAT), 24
- patient outcome measurement, 41–42
- Patient Protection and Affordable Care Act (2010), 36*t*
- Patient-Reported Oral Mucositis Symptom (PROMS) scale, 470, 471*f*
- patient-reported outcomes, in symptom review, 300, 470
- Patient-Reported Outcomes Measurement Information System (PROMIS) Sexual Interest and Satisfaction Measure (SexFS), 647, 648
- pazopanib, 163*t*–164*t*, 198
- cardiotoxicity of, 512*t*
  - endocrine toxicities from, 688*t*
  - hepatotoxicity of, 596*t*
  - ocular toxicity from, 766*t*
  - pulmonary toxicity of, 555*t*
- PDE5 inhibitors, for erectile dysfunction, 648
- pediatric patients
- oral mucositis in, 469
  - pretreatment assessment of, 298
  - second cancers in, 784–785
  - survivorship of, 773
- pegaspargase, 90*t*
- endocrine toxicities from, 686*t*
  - infusion reaction from, 387*t*
- pegfilgrastim, 414*t*, 417
- cardiotoxicity of, 520*t*
- pembrolizumab, 229*t*–232*t*
- cardiotoxicity of, 517*t*
  - colitis from, 458, 464
  - endocrine toxicities from, 689*t*
  - hepatotoxicity of, 599*t*
  - infusion reaction from, 380*t*
  - pulmonary toxicity of, 559*t*
- pemetrexed, 81*t*–82*t*
- cardiotoxicity of, 501*t*
  - genitourinary toxicity of, 618*t*
  - hepatotoxicity of, 587*t*
  - ocular toxicity of, 759*t*
  - pulmonary toxicity of, 548*t*
- pemigatinib, 164*t*, 195
- genitourinary toxicity of, 621*t*
- penile prosthetic implants, for erectile dysfunction, 649
- pentostatin, 82*t*
- cardiotoxicity of, 502*t*
  - genitourinary toxicity of, 619*t*
  - hepatotoxicity of, 587*t*
  - ocular toxicity of, 759*t*
  - pulmonary toxicity of, 548*t*
- percutaneous nephrostomy infusions, 328–331
- performance status, assessment of, 41–42, 43*t*, 299–300, 444, 570
- peripheral neuropathy (PN), 722*t*–723*t*, 735–736, 745
- peripheral venous access, 310, 313–314
- extravasation from, 360–361 (*See also* extravasation)
- peripherally acting mu-opioid receptor antagonists (PAMORAs), 479, 480*t*
- perirectal cellulitis, 475–476
- personal health literacy, 21
- personal protective equipment (PPE), 342, 344–345, 349
- pertuzumab, 267*t*–268*t*
- cardiotoxicity of, 525*t*
  - infusion reaction from, 380*t*–381*t*
  - ocular toxicity of, 763*t*
  - pulmonary toxicity of, 566*t*
- pexidartinib, 165*t*
- hepatotoxicity of, 597*t*
- pharmacokinetics, 42–43
- Philadelphia chromosome, discovery of, 35*t*
- phosphatidylinositol 3-kinase (PI3K), 193
- diarrhea from, 448
- photosensitivity, 663*t*, 672
- physical activity
- with anorexia/cachexia, 445
  - with cognitive impairment, 744
  - with fatigue, 706–708
- physical examination
- for infection, 417–418
  - pretreatment, 298, 300
- pigment changes, 660*t*, 665*t*, 675*f*
- pituitary adenomas, hormone therapy for, 107
- plant alkaloids, 92*t*–96*t*, 97–98. *See also specific agents*
- cardiotoxicity of, 502*t*–504*t*
  - hepatotoxicity of, 590*t*–591*t*
  - peripheral neuropathy from, 722*t*
  - pulmonary toxicity of, 550*t*–551*t*
- plants/flowers, with neutropenic patients, 410
- plasma cells, 205–206
- plasmapheresis, 295
- plasticity model, of cancer development, 29
- platelets, 405, 408*t*, 420. *See also* thrombocytopenia
- plerixafor, 414*t*–415*t*
- pleural effusions, 575–576
- PLISSIT model, for sexuality communication, 649
- pluripotent stem cells, 405. *See also* hematopoietic stem cells
- polatuzumab vedotin-piiq, 215*t*–216*t*
- hepatotoxicity of, 603*t*
  - infusion reaction from, 381*t*
  - pulmonary toxicity of, 566*t*
- policies and procedures, 5–6, 353–354
- poly(ADP-ribose) polymerase (PARP) inhibitors, 197
- diarrhea from, 448
- pomalidomide, 249*t*
- cardiotoxicity of, 527*t*
  - hepatotoxicity of, 601*t*
  - pulmonary toxicity of, 561*t*
- ponatinib, 113, 166*t*
- cardiotoxicity of, 513*t*
  - hepatotoxicity of, 597*t*
- positron-emission tomography (PET) assessment
- for interstitial lung disease, 571
  - of tumor response, 40
- Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST), 40
- posterior reversible encephalopathy syndrome (PRES), 720*t*, 727–728. *See also* encephalopathy
- post-therapy/post-neoadjuvant therapy, 33
- pralatrexate, 82*t*
- genitourinary toxicity of, 619*t*
  - hepatotoxicity of, 587*t*
- pralsetinib, 167*t*, 198
- hepatotoxicity of, 597*t*
  - pulmonary toxicity of, 555*t*
- precision medicine framework, for infusion reactions, 370–371, 371*f*
- precision oncology, defined, 37, 37*t*
- pregabalin, for menopausal symptoms, 647
- pregnancy
- and safe handling of HDs, 254, 341–342
  - during treatment, 298–299
- prescribing errors, 6, 7
- pretreatment assessment, 293–303
- prevention. *See* cancer prevention
- PRIDE syndrome, 669
- primary cancer prevention, 32
- primary drug resistance, 44
- priming IV tubing, 310–311
- probiotics, for diarrhea, 455, 472, 474*t*
- procarbazine, 90*t*
- hepatotoxicity of, 590*t*
  - ocular toxicity of, 760*t*
- procedures, 6. *See also* policies and procedures
- prochlorperazine, for CINV, 434, 438*t*
- professional boundaries, 16
- professional education, 3–5
- professional nursing practice, 3
- programmable implanted intra-arterial pumps, 333–334
- programmed cell death-ligand 1 (PD-L1) protein, 39, 209, 213, 557*t*–558*t*, 600*t*, 672
- programmed cell death protein 1 (PD-1), 39, 208, 213, 227*t*–235*t*, 558*t*–559*t*, 599*t*, 672
- progressive multifocal leukoencephalopathy (PML), 720*t*, 729–730. *See also* leukoencephalopathy
- prolongation-of-life decisions, ethics of, 16
- promethazine, for CINV, 438*t*
- prostaglandin E1, for erectile dysfunction, 649
- prostate cancer, hormone therapy for, 101–107
- proteasome inhibitors, 197–198, 369
- protocols, for clinical trials, 54–57, 56*f*
- proton pump inhibitor, for CINV, 433–434
- proto-oncogenes, 29
- pruritus, 664*t*, 676*t*
- pseudoprogression, 725
- psychosocial assessment
- pretreatment, 299, 303
  - with sexual dysfunction, 647
- psychosocial issues, with skin toxicities, 675
- psychosocial support, for anorexia/cachexia, 445
- pulmonary alveolar proteinosis (PAP), 544
- pulmonary edema, 544, 569
- pulmonary function tests (PFTs), 303, 571–572
- pulmonary testing, pretreatment, 303
- pulmonary toxicities, 543. *See also* APL
- treatment-related differentiation syndrome; diffuse alveolar hemorrhage; interstitial lung disease; pleural effusions
- patient education on, 576–577

## Q

QT prolongation, 296, 493, 528–529

quality control/monitoring, in professional nursing practice, 3, 9. *See also* medication errors; verification

quality of life, symptom assessment on, 41

Quality Oncology Practice Initiative Certification Program (QOPI), 9

## R

radiation fibrosis syndrome, 725–726

radiation monitoring, 350  
 radiation necrosis, 724–725  
 radiation recall, 294  
 radiation therapy, 33–34  
   constipation from, 476, 477t  
   cutaneous toxicities of, 673  
   diarrhea with, 451  
   genitourinary toxicity of, 632–633  
   history of, 35t  
   mucositis with, 468–469, 472  
   nausea/vomiting with, 430  
   neurotoxicity of, 717–725  
   pulmonary toxicity of, 545  
   second cancer risk with, 778  
 radioimmunoconjugates, 222t–223t, 284  
 radioimmunotherapy, 284, 285–286  
 radiopharmaceuticals, safe handling of, 350, 351  
 Rai staging system, 33  
 raloxifene, 106t, 109–110  
 ramucirumab, 259t–260t  
   cardiotoxicity of, 524t  
   endocrine toxicities from, 690t  
   infusion reaction from, 381t  
 rasburicase, for TLS management, 629  
 rash, 665t, 670f, 672, 672f, 673f, 674, 675, 676t–677t  
 rearranged during transfection (RET) kinase inhibitors, 198  
 receptor tyrosine kinases (RTKs), 206–207  
 RECIST guidelines, 39–40  
 recurrence, fear of, 775  
 red blood cells (RBCs), 405, 408t, 418–420  
 refractory CINV, 429, 435  
 regorafenib, 168t, 198  
   cardiotoxicity of, 514t  
   hepatotoxicity of, 597t  
 regulatory T cells, 204, 205, 207  
 relative dose intensity, calculation of, 38  
 relugolix, 105t  
 renal failure, 295  
 reproductive functioning, alterations in, 650–653  
 respirators, 345. *See also* personal protective equipment  
 response. *See* tumor response  
 Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, 39–40  
 restaging, 33  
 retinoblastoma, inter-arterial chemotherapy for, 332  
 RET kinase inhibitors, 198  
 ribociclib, 168t–169t, 193  
   cardiotoxicity of, 514t  
   hepatotoxicity of, 597t  
   pulmonary toxicity of, 556t  
 ripretinib, 169t–170t  
 rituximab, 253t–254t, 311  
   cardiotoxicity of, 523t  
   infusion reaction from, 382t, 393  
   pulmonary toxicity of, 563t  
 rolapitant, for CINV, 439t  
 romidepsin, 170t, 195  
   cardiotoxicity of, 514t  
 romiplostim, 171t, 198  
 ROS proto-oncogene (ROS1) inhibitors, 198  
 routes of chemotherapy, 308–334  
 rucaparib, 172t, 197  
 ruxolitinib, 173t, 196  
   genitourinary toxicity of, 621t

## S

sacituzumab govitecan-hziy, 220t, 283  
 safe handling, 341–344, 799–800. *See also* hazardous drugs; personal protective equipment  
   during administration, 349–350  
   of body fluids, 350–351  
   during compounding, 347–349  
   in home settings, 346f–347f, 350–351  
 safety, in professional nursing practice, 3, 6. *See also* safe handling  
 safety monitoring, 9, 795–796. *See also* safe handling  
 sargramostim, 415t  
   cardiotoxicity of, 520t  
 scalp cooling, 679–680  
*Scope and Standards of Oncology Nursing Practice* (ONS), 16  
 SC routes, for chemotherapy, 309–310  
 secondary cancer prevention, 32  
 secondary drug resistance, 44  
 second primary cancers, 778–781, 784  
 secretory diarrhea, 447  
 seizures, 720t–721t, 734–735, 745  
 selective estrogen receptor downregulators, 104t, 109  
 selective estrogen receptor modulators (SERMs), 106t, 109–110. *See also specific agents*  
 selective serotonin reuptake inhibitors, for menopausal symptoms, 647  
 selinexor, 174t, 195  
 seliperatinib, 175t, 198  
 selumetinib, 176t  
   cutaneous toxicities of, 671–672  
 septic shock, with neutropenia, 409  
 serotonin inhibitors, for CINV, 438t–440t  
 serotonin noradrenaline reuptake inhibitors, for menopausal symptoms, 647  
 Sexual Activity Questionnaire, 647  
 sexual dysfunction  
   assessment of, 649–650  
   clinical manifestations of, 646  
   incidence of, 644–645  
   management of, 646–650  
   pathophysiology of, 643–644  
   patient/partner education on, 650  
   risk factors for, 645–646  
 SIADH, 625–626  
 side effects. *See* toxicities  
 sildenafil, for erectile dysfunction, 648  
 siltuximab, infusion reaction from, 382t  
 simulation, in clinical training, 5  
 sinus dysrhythmias, 493  
 sinusoidal obstruction syndrome (SOS), 605–606, 607t  
 sipuleucel-T, 247t  
   cardiotoxicity of, 526t  
 SIR (standard infusion reaction) phenotypes, 370–371, 371f, 387–389  
 skin blistering, 665t  
 skin care  
   during diarrhea, 457  
   for infection prevention, 411, 421  
 skin depigmentation, 665t  
 skin fissures, 661t, 675f  
 skin testing, for hypersensitivity reaction, 397, 570  
 skin toxicities. *See* cutaneous toxicities  
 small molecule inhibitors, 207  
   cardiotoxicity of, 504t–517t

endocrine toxicities from, 686t–688t  
 genitourinary toxicity of, 619t–622t  
 hepatotoxicity of, 591t–599t  
 ocular toxicity from, 764t–766t  
 peripheral neuropathy from, 723t  
 SMART syndrome, 721–724  
 Society for Immunotherapy of Cancer, on immune-related adverse events, 276  
 somatic cancers, 31  
 somatostatin analogs, for diarrhea, 456t  
 sonidegib, 177t, 196  
 sorafenib, 177t–178t, 198  
   cardiotoxicity of, 514t  
   cutaneous toxicities of, 670–671  
   endocrine toxicities from, 688t  
   hepatotoxicity of, 598t  
   pulmonary toxicity of, 556t  
 sotorasib, 178t  
   hepatotoxicity of, 598t  
   pulmonary toxicity of, 556t  
 sperm cryopreservation, 652  
 spill management, of HDs, 352–353, 352f  
 spontaneous cell transformation, 31  
 staging, 33, 34f  
 standard infusion reaction (SIR) phenotypes, 370–371, 371f, 387–389. *See also* infusion-related reactions  
 steatorrhea, 448  
 steatosis, 604–605  
 stem cell mobilizers, 414t–415t  
 stem cell model, of cancer development, 29  
 steroids  
   endocrine toxicities from, 691t  
   with immunotherapy, 297  
 Stevens-Johnson syndrome, 665t  
 stimulant laxatives, 479, 481t  
 stomatitis, 467, 468. *See also* mucositis  
 stool softeners, 481t  
 storage, of hazardous drugs, 345–347  
 streptozocin, 91t  
   endocrine toxicities from, 686t  
   hepatotoxicity of, 590t  
   as irritant, 368t  
 subcutaneous (SC) routes, for chemotherapy, 309–310  
 sucralate, for proctitis, 472, 474t  
 sunitinib, 179t, 198  
   cardiotoxicity of, 515t  
   cutaneous toxicities of, 670–671  
   endocrine toxicities from, 688t  
   genitourinary toxicity of, 621t  
   hepatotoxicity of, 598t  
   ocular toxicity from, 766t  
 surgery, 33, 451  
 survival data, 41  
 survivorship care, 32–33, 773–774, 775t  
   long-term/late effects and, 775–786, 776t–777t  
   (See also second primary cancers)  
   preventive health in, 786  
 syndrome of inappropriate antidiuretic hormone secretion (SIADH), 625–626

## T

tacrolimus  
   endocrine toxicities from, 690t  
   ocular toxicity of, 764t  
 tadalafil, for erectile dysfunction, 648



- tafasitamab-cxix, 268t  
   infusion reaction from, 382t–383t  
   pulmonary toxicity of, 566t  
 tagraxofusp-erzs, 223t–224t  
   hepatotoxicity of, 601t  
 talazoparib, 180t, 197  
   genitourinary toxicity of, 622t  
 talimogene laherparepvec, 273t–274t  
 tamoxifen, 106t, 109–110  
   ocular toxicity of, 761t  
 targeted therapies, 15–16, 35–39, 37t, 113, 114t–192t. *See also specific agents*  
   adverse effects of, 114t–192t, 199, 199f, 369  
   cardiotoxicity of, 493, 535  
   constipation from, 478f  
   cutaneous toxicities of, 673  
   diarrhea from, 447–448, 449f–450f, 451, 454–455  
   endocrine toxicities from, 686t–688t  
   genitourinary toxicities of, 616, 619t–622t  
   hepatotoxicity of, 591t–599t  
   nausea/vomiting with, 429f–430f, 430  
   ocular toxicity of, 764t–766t  
   peripheral neuropathy from, 722t–723t  
   pulmonary toxicity of, 551t–557t  
   sexual dysfunction from, 645  
   stomatitis from, 468  
 taxanes, 93t–95t, 98. *See also specific agents*  
   cardiotoxicity of, 502t–503t  
   cutaneous toxicities of, 657  
   diarrhea from, 448  
   extravasation of, 359–360, 364t, 365  
   hepatotoxicity of, 590t–591t  
   neurotoxicity of, 737–738  
   ocular toxicity of, 760t  
   pulmonary toxicity of, 550t–551t  
 tazemetostat, 180t, 195  
 tbo-filgrastim, 413t, 417  
 T cells, 205, 207, 408t  
 teach-back techniques, in patient education, 24, 299  
 tebentafusp-tebn, 181t  
 telangiectasia, 666t  
 telogen effluvium, 677. *See also alopecia*  
 temozolomide, 74t  
   hepatotoxicity of, 586t  
   pulmonary toxicity of, 547t  
 temporary percutaneous catheters, 333  
 temsirolimus, 181t–182t, 197  
   cardiotoxicity of, 515t  
   endocrine toxicities from, 688t  
   genitourinary toxicity of, 621t  
   hepatotoxicity of, 598t  
   pulmonary toxicity of, 556t  
 teniposide, 93t  
 tepotinib, 183t, 197  
   pulmonary toxicity of, 556t  
 tertiary cancer prevention, 32  
 thalidomide, 250t  
   cardiotoxicity of, 527t  
   hepatotoxicity of, 601t  
   neurotoxicity of, 738  
   pulmonary toxicity of, 561t  
 thioguanine, 82t  
   hepatotoxicity of, 588t  
 thiotepa, 74t  
   genitourinary toxicities with, 632  
 thrombocytopenia, 405, 406t, 420–421  
 thromboembolism, 718t, 732–733  
 thrombopoiesis, 420  
 thrombopoietic growth factor, 415t  
 thrombopoietin (TPO) receptor agonists, 198  
 thyroid cancer, hormone therapy for, 107  
 thyroid disorders, 691–696  
 thyroid function tests, pretreatment, 302  
 time to treatment failure, 41  
 tincture of opium, for diarrhea, 454  
 tipiracil, 79t  
 tisagenlecleucel, 243t–244t, 277  
   cardiotoxicity of, 519t  
 tisotumab vedotin, 756  
 tissue mast cells, 408t  
 tivozanib, 183t–184t  
   cardiotoxicity of, 515t  
   endocrine toxicities from, 688t  
 TNM staging system, 33, 34f  
 tocilizumab, 278  
 tofacitinib, 196  
 tolvaptan, for AKI, 626  
 topotecan, 92t  
   cutaneous toxicities of, 657  
   hepatotoxicity of, 591t  
   as irritant, 368t  
   pulmonary toxicity of, 549t  
 toxic epidermal necrolysis, 666t  
 toxic erythema of chemotherapy, 669  
 toxicities. *See also specific agents*  
   of checkpoint inhibitors, 276–280  
   of oncolytic viral immunotherapies, 286–287  
   by system, 97f, 101f, 199f, 276f  
 TPO receptor agonists, 198  
 trabectedin, 75t  
   cardiotoxicity of, 496t  
   extravasation of, 363t  
   hepatotoxicity of, 586t  
 trametinib, 184t, 193  
   cardiotoxicity of, 516t  
   cutaneous toxicities of, 671–672  
   endocrine toxicities from, 688t  
   genitourinary toxicity of, 622t  
   hepatotoxicity of, 598t  
   ocular toxicity from, 766t  
   pulmonary toxicity of, 556t–557t  
 transgender patients, 299  
 transhepatic arterial chemoembolization (TACE), 331  
 transient erythema, 667t  
 trastuzumab, 267t–270t, 269t, 283  
   cardiotoxicity of, 525t, 536  
   diarrhea from, 448  
   infusion reaction from, 383t  
   ocular toxicity of, 763t  
   pulmonary toxicity of, 566t, 567t  
 trastuzumab-pkrb, 269t  
 treatment cycles, dosing in, 38  
 treatment goals, 32, 293  
 treatment modalities, 33–37, 35t–36t  
 treatment summaries, 9  
 tretinoin, 87t  
 trichomegaly, 667t, 674f  
 trifluridine, 79t  
 trilaciclib, 411, 416t  
 triptorelin, 105t  
 Trousseau sign, 629  
 tubing  
   priming, 310–311  
   selection of, 312–313  
 tucatinib, 185t, 196  
   genitourinary toxicity of, 622t  
   hepatotoxicity of, 598t  
 tumor, node, metastasis (TNM) staging system, 33, 34f  
 tumor burden, defined, 42  
 tumor doubling time, 67  
 tumor escape mechanisms, theories of, 208–209  
 tumor flare, 108  
 tumor grade, 33. *See also grading*  
 tumor growth fraction, 67  
 tumor heterogeneity, defined, 44  
 tumor kinetics, 67  
 tumor lysis syndrome (TLS), 626–629  
 tumor response  
   to chemotherapy, 39–40  
   factors affecting, 42–44  
 tumor suppressor genes, 29, 37t  
 tumor suppressor protein p53 (TP53), 44  
 typhlitis, 448, 457–458. *See also colitis*  
 tyrosine kinase inhibitors (TKIs), 113, 193f, 194f, 443  
   diarrhea from, 448  
   endocrine toxicities from, 692–693  
   pulmonary toxicity of, 569
- ## U
- umbralisib, 186t, 193  
   hepatotoxicity of, 599t  
 unconjugated mAbs, 283. *See also monoclonal antibodies*  
 underweight patients, dosing for, 305  
 uridine triacetate, for diarrhea, 455  
 urticaria, 667t  
 uterine cancer, hormone therapy for, 107
- ## V
- vacuum erection devices, for erectile dysfunction, 648–649  
 vaginal stenosis, 644  
 valrubicin, 87t  
   endocrine toxicities from, 686t  
 vandetanib, 186t–187t  
   cardiotoxicity of, 516t  
   endocrine toxicities from, 688t  
   genitourinary toxicity of, 622t  
   hepatotoxicity of, 599t  
   ocular toxicity from, 766t  
   pulmonary toxicity of, 557t  
 vardenafil, for erectile dysfunction, 648  
 variants, pathogenic, 29–31  
 vascular endothelial growth factor (VEGF) receptor, 193–194, 194f  
 VEGF inhibitors, 198  
 VEGF receptors, 193–194, 194f  
 vein irritation, from infusion, 359, 361, 366–370, 367t–368t  
 vemurafenib, 187t–188t, 193  
   cardiotoxicity of, 517t  
   cutaneous toxicities of, 671–672  
   genitourinary toxicity of, 622t  
   hepatotoxicity of, 599t  
   ocular toxicity from, 766t  
 venetoclax, 188t–189t, 197



veno-occlusive disease. *See* hepatic sinusoidal obstruction syndrome (SOS)

venous thromboembolism (VTE), 532

ventricular arrhythmias, 493

veracity, 17*t*

verification process, steps in, 306–308

vesicants

- extravasation of, 359–361 (*See also* extravasation)
- pathophysiology of, 359
- safety management of, 8 (*See also* safe handling)

vinblastine, 95*t*

- cardiotoxicity of, 503*t*
- extravasation of, 364*t*
- ocular toxicity of, 761*t*

vinca alkaloids, 95*t*–96*t*, 98, 311. *See also* specific agents

- cardiotoxicity of, 504*t*
- extravasation of, 359, 364*t*, 365
- hepatotoxicity of, 591*t*
- neurotoxicity of, 736–737
- ocular toxicity of, 761*t*
- pulmonary toxicity of, 551*t*
- sexual dysfunction from, 645

vincristine, 95*t*–96*t*

- cardiotoxicity of, 504*t*
- extravasation of, 364*t*
- hepatotoxicity of, 591*t*
- neurotoxicity of, 737
- ocular toxicity of, 761*t*

vinorelbine, 96*t*

- cardiotoxicity of, 504*t*
- extravasation of, 364*t*, 370
- as irritant, 369–370
- pulmonary toxicity of, 551*t*

viruses, cancer development from, 31

vismodegib, 190*t*, 196

vital signs, pretreatment review of, 300

vitiligo, 665*t*

vomiting center (VC), 425, 426*f*, 427–428

vorinostat, 190*t*, 195

- cardiotoxicity of, 517*t*
- endocrine toxicities from, 686*t*, 688*t*

## W

weight

- dosing calculations and, 304–305, 305*f*
- pretreatment assessment of, 300

weight-based dosing, 303, 306

white blood cells (WBCs), 405, 408

WHO performance status scale. *See* ECOG Performance Status Scale

wigs, 681

World Health Organization (WHO)

- Oral Toxicity Scale, 470
- performance status scale (*See* ECOG Performance Status Scale)

## X

xerosis, 668*t*, 676*t*

XPO1 inhibitors, 195

## Z

zanubrutinib, 191*t*, 193

- cardiotoxicity of, 517*t*

ziv-aflibercept, 192*t*, 198

- cardiotoxicity of, 517*t*

zoledronic acid, genitourinary toxicity of, 623, 623*t*

Zubrod score. *See* ECOG Performance Status Scale















Oncology nursing is a unique specialty that requires continuous learning to stay current on cancer pathophysiology, cutting-edge drugs, and the evidence-based management of cancer and its treatment-related toxicities. The Oncology Nursing Society's *Chemotherapy and Immunotherapy Guidelines and Recommendations for Practice* (second edition) provides nurses with the tools to understand how medications are used in cancer treatment, the effect of medication-related toxicities, and evidence-based recommendations to manage and treat these toxicities. This edition features many new cancer therapies approved since the 2019 publication. Extensive drug tables provide nurses with categorical drug information based on treatment type and tips for managing patients receiving these treatments.

New evidence relating to cancer nursing care is incorporated into this edition, such as hypersensitivity response, safe handling of hazardous drugs, and more. Expanded content on genomics corresponds with the progress made toward personalized oncology. Health equity is approached with information discussing financial distress, cultural disparities, and health literacy. The latest guidelines and recommendations for treatment, symptom management, and survivorship are also included.

A QR code is provided with the purchase of this book, allowing access to periodic drug updates.



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