Theranostics: Now and in the Future

Daniel Lee, MD
Department of Radiology, Ochsner Medical Center

As President of the Therapy Center of Excellence, I am pleased to introduce this special Pathways Newsletter dedicated to Theranostics. The FDA’s recent approval of \(^{68}\text{Ga-DOTATATE}\) and \(^{177}\text{Lu-DOTATATE}\) was met with much anticipation and excitement by neuroendocrine tumor (NET) patients and the nuclear medicine community. The excitement has not abated as ever more sites work toward offering Peptide Receptor Radionuclide Therapy (PRRT), and we have assembled a great team of authors to share their experience so that you too can offer theranostics at your facility.

Beyond the ability to obtain \(^{68}\text{Ga-DOTATATE}\) and \(^{177}\text{Lu-DOTATATE}\), an institution must have the appropriate resources to manage NET patients. Such resources include a multidisciplinary team of medical oncologists, surgical oncologists, interventional oncologists, nuclear medicine physicians, and nurses to consider the available local and systemic treatment modalities. If and when the decision has been made for PRRT, administrators, technologists, pharmacists, schedulers, billing and coding personnel, and radiation safety personnel come into the picture. As described by Rhiney Hampton and Amanda Abbott, successful coordination of PRRT is a concerted effort that involves planning and forethought to anticipate needs before, during, and after the entire process; the ability to adapt to unforeseen circumstances; and the ability to learn from experience.

New theranostic agents may also come with additional challenges. For example, the enormous demand for \(^{68}\text{Ga-DOTATATE}\) PET/CT for NET imaging has taxed the supply of generators and brought about the search for alternate positron-emitting radionuclides to label DOTATATE. There may also be compliance matters such as a facility’s need to amend its RAM license to accommodate the new radionuclides, and long-lived byproducts such as Lu-177m may stretch a facility’s capacity for decay-in-storage and radioactive waste disposal, a matter discussed by Eric Hendersen. Additionally, the NRC must determine the appropriate qualifications for Authorized Users, and a facility must be staffed by personnel with the appropriate status. Beyond supply and regulatory concerns, financial matters related to radionuclide therapies must also be addressed. The cost and coverage of radionuclide therapies raises questions about accessibility for patients, and adequate reimbursement is necessary to be fiscally sustainable for treating facilities.

As for future theranostics, there is arguably even greater anticipation for the prostate cancer theranostic agents, \(^{68}\text{Ga-PSMA}\) and \(^{177}\text{Lu-PSMA}\). These are nearing the end of their Phase III evaluation in the VISION trial, and there is optimism for FDA approval to provide additional treatment options for the most common malignancy in men. There is also reason for continued optimism and excitement beyond PSMA. Why? Because of the pipeline of ongoing development of new diagnostic and therapeutic agents. Positron-emitters with longer...
The rapid adoption and growth of targeted radionuclide therapy (TRT) is transforming the approach to treating cancer in the United States (US). Sites all over the US are initiating the practice of TRT with the first wave of approved agents, including Xofigo®([223Ra]radium dichloride, Lutathera®([177Lu]DOTATATE, and Azedra®([131I] MIBG). The field is anticipating the second wave that is expected to include PSMA analogs for imaging and treating prostate cancer and additional neuroendocrine tumor-targeting agents. Early published results of PSMA therapies coming out of Europe and Australia are highly promising. With the introduction of PSMA-based therapies and other soon-to-follow agents, it is inevitable that TRT will expand beyond orphan indications and “treatment of last resort” into other mainstream cancers and earlier interventions. As this occurs, we, as a professional society, need to anticipate and to lead the response to the technological, professional, and regulatory challenges that lie ahead.

As we prepare for potentially paradigm-changing treatments for a common cancer affecting millions of men in the US (and other cancers as new agents approach approval), we would be wise to consider the potential of optimizing prescribed dose based upon personalized dosimetry. To date, all FDA-approved TRT agents in the US implement a simplified prescribed dose schema that does not account for potential dose optimization and personalization (e.g., maximized dose to tumor while avoiding toxic doses to critical organs). However, given current PET and SPECT quantitative imaging capabilities, sophisticated treatment planning strategies more akin to external beam radiation therapy can be implemented. This approach likely requires phase 1 and 2 clinical trials to incorporate quantitative imaging-based methods into the trial design to provide clear data supporting the efficacy of this approach.

Adoption of personalized dosimetry for TRT requires additional technological and administrative developments in nuclear medicine including simplifying imaging protocols that currently require multiple post-infusion visits; validated, commercially-available quantitative dosimetry software; and a reimbursement approach that covers the personnel and infrastructure costs associated with both therapy-related imaging and dosimetric calculations. There are clear precedents for this approach in related fields. Radiation oncology has integrated reimbursable imaging and dosimetry workflows into their clinical external beam radiation therapy practice model largely through the efforts of sister professional organizations including the American Society for Radiation Oncology (ASTRO) and the American Association of Physicists in Medicine (AAPM). Currently, nuclear medicine physicists do not have the ability to bill for such work, but SNMMI is working to resolve this discrepancy.

The rapid growth in theranostics and TRT also highlights the critical need to prepare the next generation of nuclear medicine physicians, physicists, and technologists to incorporate current and developing TRTs in their practice. The question of who is qualified to prescribe and administer TRTs is an open question currently under debate. This is particularly important as enthusiasm for TRT is expanding beyond nuclear medicine and into adjacent fields of radiation and medical oncology. It is likely that a new training curriculum for currently practicing physicians needs to be developed; a parallel situation exists for physicists. SNMMI is actively interfacing with both ASTRO and AAPM in inter-societal initiatives to tackle these issues in cooperative ventures.

These are exciting times for the field of nuclear medicine and TRT as dozens of new agents are in early phase trials for cancer therapy. Emerging approaches include using alpha-emitting radionuclides and coupling TRT with immunotherapy, which may enhance efficacy without increasing toxicity. Despite these successes, accurate dosimetry and basic radiobiology questions remain unanswered. At conferences such as the 3rd Targeted Radionuclide Therapy Conference held in December 2019, co-sponsored by SNMMI and NCI, we continue to explore solutions and develop cooperative approaches to answering these questions and improving the care of cancer patients through TRT.
Nuts and Bolts: Site Set-up for Lutathera® Infusions

Amanda Abbott, MS, CNMT, RT(N)(CT), PET
Imaging Research Manager, Dana-Farber Cancer Institute
Tech Chair, CTN Education Committee

Preparation and implementation procedures required for lutetium Lu 177 dotatate (Lutathera®) Peptide Receptor Radionuclide Therapy (PRRT) administration and patient care are more complex than most routine nuclear medicine techniques and therapies administered in nuclear medicine departments. Consider the six key factors below when planning successful implementation of a Lutathera PRRT program.

Who: The team is multidisciplinary. Key players include nuclear medicine physicians, nuclear medicine technologists, radiation safety professionals, medical oncologists, radiation oncologists, pharmacists, nurses, physicists, revenue integrity (finance), and a program coordinator. Nuclear medicine physicians and oncologists would ideally join in regular tumor boards to evaluate patients and discuss appropriate treatment options. A consultation with the nuclear medicine physician should precede the treatment day so as to review the procedure and radiation safety instructions with the patient and answer all questions. Close patient care is required throughout treatment starting with the first treatment day when a designated nuclear medicine technologist and nurse attend to the patient throughout that day.

What: There are several preparation steps for the site, the nuclear medicine department, and patients, including the training required for each step to be successful.

1. Site (facility)
   • Develop new processes for ordering the dose and medications
   • Set up a schedule to include all patient activities
   • Determine the methods required to bill payors/providers

2. Nuclear medicine department
   • Add 177Lu to the Radioactive Materials (RAM) license
   • Calibrate the dose calibrator for 177Lu
   • Make resources available as applicable (e.g., treatment rooms, patient restrooms, supplies, staff)

3. Patients
   • Review radiation safety instructions and acknowledge understanding. Ask questions.
   • Required imaging may be done at different points during your treatment.
   • Just prior to treatment, change into scrubs and get as comfortable as possible.

   • Take antiemetic premedication and amino acids infusion for radioprotection of the kidneys. Note to Provider: The amino acids available commercially include other substances that increase emetic effects, while the compounded version only includes the required amounts of lysine/arginine with little to no emetic effects.

4. Training is tailored to each member’s role on the team. Developing an overall workflow training schedule and checklist is helpful. Technologists may need therapy simulation exercises using saline and food coloring as training for dose preparation. Radiation safety training includes review of precautions specific to 177Lu and its contaminant, 177mLu. See “Lutathera® Waste: A Disposal Dilemma” in this newsletter for more information on waste storage and proper waste disposal.

When: Order the dose two weeks in advance. Patients receiving somatostatin analogue therapy should discontinue the long-acting therapy at least four weeks in advance, and at least 24 hours in advance if using the short-acting therapy. The entire procedure lasts approximately five to eight hours, depending on which amino acid infusion is administered. The compounded preparation is infused over four hours while the commercial preparation is infused over six-plus hours.

Where: Sites need to decide what procedures take place where in their facility. The three key procedures—therapy infusion, concomitant medication administration, and patient care—can be done in the nuclear medicine department, in an oncology clinic or in a radiation oncology setting; perhaps a combination of the three works best for your site.

How: The dose can be administered either from the vial or from a syringe. The treatment room and patient restroom is prepared in advance to prevent radiation contamination.

Why: For the patients, of course! It is wonderful to have this therapeutic option available for them.

With adequate planning and preparation, your site can safely and successfully administer Lutathera.

References
Peptide Receptor Radionuclide Therapy (PRRT) administration of lutetium Lu 177 dotatate (Lutathera®) incurs some additional operational challenges for the disposal of radioactive waste at the site. This article focuses on concerns posed by the management of an unavoidable contaminant.

The Problem

The production of radioactive lutetium-177 (Lu-177 or \(^{177}\text{Lu}\), half-life = 6.65 days) by neutron irradiation of natural or enriched lutetium targets\(^1\) intrinsically yields co-production of Lu-177m, a chemically-indistinguishable contaminant with a significantly longer half-life (>160 days). The relative concentration in the delivered product is very low, nominally < 0.02% of the delivered activity\(^2\), but most licensees are not authorized to retain waste with half-lives longer than 120 days.

Before & After Dose Administration

Roughly 44% (up to 88 mCi) of the administered dose is excreted in urine within five hours after dose administration while patients are still receiving amino acids infusion and monitoring (see “Nuts and Bolts: Site Set-up for Lutathera® Infusions” in this newsletter). If successfully directed to the sanitary sewer, the excreta are exempt from regulatory constraints. However, if this option isn’t possible, there could be enough transferable activity and high enough external exposure rate that the treatment room may not be usable again for quite some time unless aggressive decontamination is performed. The labor costs, supplies and room “down time” for decontamination warrants preparatory measures to isolate and contain incidental releases.

Covering nearby surfaces with an impermeable lining (e.g., poly-backed Kraft paper) can minimize the potential severity of a contamination incident, but this also adds to the waste volume requiring space, management and, ultimately, Low Level Waste (LLW) cost. As the sacrificial coverings are removed, thoroughly survey the area to selectively segregate the contaminated materials and minimize the waste volume for decay/disposal. Patients exhibiting or communicating urinary urgency or incontinence may require additional preparation to prevent persistent contamination of seating surfaces. Urine-soaked linens, scrubs or diapers may be treated with superabsorbent material (e.g., sodium polyacrylate) to prevent leakage or dripping during storage, handling and transport.

Waste Management / Release Criteria

Regulations relating to “decay-in-storage” (DIS) release criteria specify surveying and screening the surface of the waste container in a low background area using instruments sensitive to the radiation of concern. The U.S. Nuclear Regulatory Commission (NRC) bulletin “LICENSING OF LUTETIUM-177 (STC-18-042)” states: “If Lu-177m is detected by appropriate survey methods, then licensees must dispose of the waste material as low-level radioactive waste in accordance with the requirements in 10 CFR Part 20 Subpart K, Waste Disposal.\(^2\) Of course, Agreement State licensees are subject to (at least) equivalent regulations. Package or container geometry is an important factor here. A large waste container has the potential to render sources deep inside invisible to detection by standard instruments such as a GM “pancake” detector or thin-crystal scintillator. When the package reaches its final end, depending on the process used to accomplish this, the material may become discoverable again, triggering undesirable responses from regulators and/or commercial operators.

Recommendations

Each facility should evaluate their own radioactive waste management processes to assess the appropriateness of their screening techniques. Judicious, experience-based preparation of dose administration areas (floor, lower walls, chair, tray table, etc.) as well as where the patient performs sanitary activities can help to minimize the possibility of contamination that might hinder subsequent use of the area. Selection of a larger-volume scintillation detector to improve screening sensitivity should be weighed against practicality. Response to materials triggering detectors at transfer stations, landfills, or a processor of regulated medical waste, etc., can be significantly less desirable than the purchase and maintenance of such an instrument.

References


Care Coordination for PRRT Infusions: Improving Efficiency

Rhiney Hampton, CNMT
Radiology Manager, Ochsner Medical Center-Kenner, Louisiana

Peptide Receptor Radionuclide Therapy (PRRT) involves extensive and coordinated planning by a multidisciplinary team of trained professionals. Unnecessary delays may occur on the day of treatment that can greatly impact efficiency and outcome and cause needless stress and anxiety for the patient. Based upon our facility’s experience in providing PRRT, we have assembled some suggestions that may help improve efficiency in your department or facility.

Assemble the team
• All team members must be knowledgeable and efficient in their assigned tasks for PRRT administration.
• The team should review, in advance, all processes and procedures involved with patient preparation and drug delivery on a given treatment day.
• Provide additional training where needed, especially with IV placements. Since it is preferable for patients to have two IVs (one in each arm), this process must go smoothly.

Manage multiple patients on a single treatment day
• Schedule the initial consultation for new patients with the nuclear medicine physician before the first scheduled treatment day to address all concerns and answer patient questions.
• Review the scheduled appointments for patients’ treatments in advance to determine what your expected time might be for each one; i.e., new vs established patient.
• Consider setting up your schedule to reserve the first two patient spots of the day for established returning patients, followed by one new and one established patient every 15 minutes. Scheduling in this fashion gives a nurse or technologist time to answer questions from new patients and limits the time that recurring patients have to spend in the department. This method of scheduling has worked extremely well for our department.

Review antiemetics and amino acids administration procedures
• Doses should be ordered and prepared prior to the patient’s arrival.
• Preferably, doses should be in the pyxis or the infusion suite before the patient is set for treatment.

Release of treatment drugs from the pharmacy
• Provide all necessary information to the pharmacy in advance.
• Essential information includes the ordering physician’s name, the drug order, patient height and weight, and day and time of treatment
• Prior to the day of administration, confirm with the pharmacy that there are no issues with releasing the drugs for the patients scheduled on the PRRT administration date.

Examine health information documentation
• Determine what consents are required for each patient – just one or all four treatments.
• Review the patient information and consents with the radiologist or authorized user scheduled to be on site for the treatment day.
• Always confirm that the consents are signed and in the chart the day before or no later than the morning of the treatment day.

The processes listed above do not comprise all instances that could affect efficiency. However, we have found that they are common causes of unnecessary delays. The PRRT administration and treatment process, if done in the projected planned timeframe, should last no longer than five hours from start to finish if administering compounded amino acids or seven to eight hours if receiving commercial amino acids. Evaluate your own facility. Take one day to conduct a thorough review of the intake and treatment process and determine how much time a patient spends from beginning to end for their procedure. Identify ways to improve the process and establish a better and more efficient visit with less stress for future patients. These tips may help you accomplish that goal.
Be Informed: Theranostics is Here to Stay
Seyed Mohammadi, CNMT, RT(N)(CT), PET
UPMC Department of Radiology – Pittsburgh, PA

Theranostics was born more than 75 years ago when the first patient received radioactive iodine-131 (I-131, atomic cocktail) for thyroid therapy by Dr. Saul Hertz in 1941. This became the building block of what we know today as “Theranostics” or Molecular Targeted Therapy. Theranostics uses specific biological pathways in the human body to deliver a therapeutic dose of radiation to the patient and acquire diagnostic images (Fig. 1). A number of these specialized targeted radiopharmaceuticals and therapies have been approved by the FDA, with more in the pipeline moving towards approval.

Theranostics requires teamwork. For example, $^{177}$Lu-DOTATATE PRRT administration requires close collaboration with a number of departments and specialists who all play a role in delivering this therapy.1,2 You don’t know when you might see a patient with Grave’s disease, Hodgkin’s lymphoma or palliative bone pain—as well as other diseases—who may qualify for targeted radionuclide therapy.

Not only must you be knowledgeable on how to help implement patient-targeted treatments and be skilled in imaging, your ability to help educate the patient on what to expect during the procedure is very important. Depending on how your facility operates, you may be one of the first persons a patient encounters on their road to treatment. Don’t use “tech-speak”—think of them as your family and how you would want them treated. Patients are not always going to remember things; providing written instructions and additional resource information may actually help you when imaging has to be performed during the therapy.

Because imaging is a vital part of treatment, always review the protocol carefully and ask questions if not sure of the parameters. Your skill at imaging a tumor before or during treatment becomes a vital part of that patient’s care. In addition to your facility’s training, you can check out the SNMMI Learning Center (www.snmmilearningcenter.org) for available courses. Also check with your accrediting body or professional association for local and national meetings that include theranostics. Don’t be left out—specialized medicine is here to stay.

References
Resources on Theranostics

**SNMMI Meetings and Conferences**

- **SNMMI and NCI Third Targeted Radionuclide Therapy (TRT) Conference.** December 16, 2019. The conference focused on maximizing dose to tumor while sparing normal tissue, the current state of the science, state of the art clinical trial design, and strategies for achieving response. View the conference slides at [www.snmmi.org/3TRT](http://www.snmmi.org/3TRT).


- **Theranostics: Regulatory Considerations for Product Development.** SNMMI 2019 Annual Meeting.

**SNMMI Resources**

- **SNMMI Learning Center:** [www.snmmilearningcenter.org/OnlineEducation.aspx](http://www.snmmilearningcenter.org/OnlineEducation.aspx)

- **SNMMI Procedure Standards:** [www.snmmi.org/ProcedureStandards](http://www.snmmi.org/ProcedureStandards)

- **SNMMI Dose Optimization Resources:** [www.snmmi.org/DoseOptimization](http://www.snmmi.org/DoseOptimization)

**Regulatory Oversight Resources**

- **LICENSING OF LUTETIUM-177 (STC-18-042) June 21, 2018.** [https://scp.nrc.gov/licensing lutetium](https://scp.nrc.gov/licensing lutetium)

- **Federal Code of Regulations, Title 10 Part 35. Medical Use of Byproduct Materials.** [https://www.nrc.gov/part035](https://www.nrc.gov/part035)

- **US Nuclear Regulatory Commission Policy Statement.** [NRC Policy Statement](https://www.nrc.gov/docs/memorandum)

- **Memorandum of Understanding between the U.S. Nuclear Regulatory Commission and the U.S. DHHS Food and Drug Administration.** [https://www.nrc.gov/docs/memorandum](https://www.nrc.gov/docs/memorandum)

**Suggested JNM Publications** *(not a comprehensive list)*


**CTN Resources for Imaging and Theranostics** [www.snmmi.org/CTN](http://www.snmmi.org/CTN)

The Clinical Trials Network continually strives to facilitate approval of new radiopharmaceuticals by working with researchers, physicians, pharma and other groups. Most recently, it liaised with the FDA and NCI to help organize and co-host the “Third Targeted Radionuclide Therapy (TRT) Conference” at the National Cancer Institute on December 16, 2019. You can view the following content from the 2018 SNMMI and NCI Theranostics Consensus Conference.

- **Day 1:** [www.snmmi.org/Consensus_Conference_Day1](http://www.snmmi.org/Consensus_Conference_Day1)
- **Day 2:** [www.snmmi.org/Consensus_Conference_Day2](http://www.snmmi.org/Consensus_Conference_Day2)
- **SNMMI and NCI Theranostics Consensus Conference.** *J Nucl Med.* 2018;60(2):7N.

CTN has also developed a number of educational resources on the topic of theranostics including live webinars (recorded) and courses for nuclear medicine imaging personnel. It has sponsored sessions at SNMMI national and local meetings and co-hosted the Theranostics: Regulatory Considerations for Product Development categorial at the SNMMI 2019 Annual Meeting. The CTN webinar series for 2019 presented timely topics on the review of radiopharmaceuticals in different clinical uses including radiotherapy. All webinars are recorded and available in the SNMMI Learning Center. Check out all available offerings on theranostics and targeted radiotherapy at [www.snmmilearningcenter.org](http://www.snmmilearningcenter.org).
SNMMI Therapy Center of Excellence

The Therapy Center of Excellence is an organizational component within the SNMMI dedicated to all aspects of the development and utilization of Targeted Radioisotope Therapy (TRT) as an alternative to other treatments. Specifically, this center brings together a centralized group of all constituents within this area creating a multi-disciplinary interest group whereby industry, big pharma, physicians, scientists, government and regulatory agencies as well as other stakeholders can convene to share ideas, develop education offerings and advance the utilization of radionuclide therapy.

The Therapy Center of Excellence:

- Provides a forum for members with similar interests
- Provides expertise in TRT
- Fosters research and education in TRT
- Provides outreach to other professionals and organizations
- Nurtures new membership in SNMMI

We face a variety of challenges as we work to advance the field of TRT. We need greater visibility and recognition for the entire field of nuclear medicine in general and of our roles in cancer patient management in particular. Just as interventional oncologists have taken a seat at the table with medical, surgical and radiation oncologists, we need to take a seat as nuclear oncologists. To that end, we need the clinical knowledge of an increasingly larger array of cancers and of relevant clinical trial data. We need innovators to create new therapeutic radiopharmaceuticals and investigators to design and conduct rigorous trials to explore additional indications for radionuclide therapy. Our goal is to help facilitate expansion of and provide support for the use of targeted radionuclide therapies to cure our patients and to alleviate their suffering. Visit our website for updates and additional information – SNMMI Therapy Center of Excellence.

Introducing “PAT”—SNMMI’s PET/CT Phantom Analysis Toolkit—Free for SNMMI Members!

SNMMI’s new cloud-based automated Phantom Analysis Toolkit (PAT) is designed to provide rapid, reliable, and reproducible fully automated phantom analysis for the four most common PET phantoms currently in use for clinical trials and clinical practice.

How it works:

1. Name your Upload/Analysis
2. Select the phantom type (ACR PET Phantom, CTN Oncology Phantom, NEMA Image Quality Phantom, or Uniform Phantom)
3. Select and Upload the phantom DICOM image files
4. Enter the phantom radioactivity fill and time data
5. Submit for analysis
6. Complete analysis back in just a few minutes. (Note: analysis time depends upon both cloud server and the size of the phantom data set.)

Meet your program accreditation requirements—check out “PAT” today!

www.snmmi.org/PAT