Examining the Clinical and Cost-Effectiveness in Managing Chemotherapy-Induced Severe Neutropenia

Faculty

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Disclosures

Dr. Fausel: Expert Witness — Dr. Reddy’s Laboratory

Dr. Adams: Has no financial relationships to disclose relating to the subject matter of this presentation.
Learning Objectives

• Explain evidence-based guidelines and recommendations for the use of prophylactic therapies within the management of chemotherapy-induced severe neutropenia
• Outline efficacy and cost data of therapies for the management of chemotherapy-induced severe neutropenia, with respect to risk and duration reduction, length of hospitalization, indirect costs, and mortality
• Distinguish among available G-CSF agents, including data on safety, administration, and costs
• Translate evidence-based guidelines and recommendations, clinical effectiveness data, and health economics research in chemotherapy-induced severe neutropenia to optimize patient-centered and value-based care decisions

G-CSF = granulocyte colony-stimulating factor.

Febrile Neutropenia

• >60,000 admissions annually in the United States
• Approximately 6% of adults receiving chemotherapy for solid tumors
• Risk higher in those with hematologic malignancies
• In-hospital mortality rate: 6.8% to 10.6%
• Cost per hospitalization: $13,372 to $22,839
• 60,000 admissions x $22,839 per admission = $1,370,340,000/year


Impact on Therapy

• 20% to 56% of patients receive <85% of planned-dose intensity
• 25% of patients have treatment delays ≥7 days
• 37% of patients have dose reductions ≥15%

Full dose on time – Approach for curable patients

Guideline HELP Is Available

- National Comprehensive Cancer Network®
  - Updated 2016
- American Society of Clinical Oncology (ASCO®)
  - Updated 2015
- European Organisation for Research and Treatment of Cancer (EORTC)
  - Updated 2010

All agree to use CSFs when risk for FN is ≥20%

FN = febrile neutropenia.


Clinical Case

- A 38-year-old white woman presents to the clinic with fever of unknown origin
- History of present illness: She was diagnosed with “triple negative” invasive stage III breast cancer (T3, No, Mo) approximately 4 weeks ago
- She received cycle 1 of doxorubicin/cyclophosphamide (AC) as neoadjuvant therapy 6 days ago
- She has an biopsy lesion that has healed from an MRSA infection – 14 days of vancomycin completed 8 days ago
- The decision is made to admit her for work-up and antibiotics

MRSA = methicillin-resistant Staphylococcus aureus.

Clinical Case (cont)

- Wt = 138 lb  Ht = 5’6”
- Vitals
  - T (current/24-hour range): 99.6/99.6-102.0
  - BP (current): 119/81
  - RR (current): 14
  - SAT (current): 95
- Laboratory results
  - ANC = 100
  - Ca = 8.5 mg/dL, Mag = 2.5 mEq/L, Phos = 4.2 mg/dL, Uric acid = 1.5 mg/dL
  - AST = 24 U/L, ALT = 13 U/L, Alk Phos = 56 U/L, Bili = 0.3 mg/dL, Albumin = 2.3 g/dL

ANC = absolute neutrophil count; AST = aspartate aminotransferase; ALT = alanine transaminase.

Clinical Case (cont)

• CXR findings
  – No definite airspace opacification is seen to suggest pneumonia
  – The tip of the left PICC line is in the area of the distal left brachiocephalic vein

• Culture results
  – Blood cultures from PICC X 1 and peripheral X 1 drawn 30 minutes apart: Results pending
  – Urinalysis: (-) WBCs, (-) nitrites, (-) leukocyte esterase, (-) bacteria
  – Urine culture: No growth to date (day 1)
  – Resistant organism: Confirmed prior wound culture was MRSA +

Empiric Antibiotics for FN

Process
• Risk assessment: High or low
• Prior resistant organisms
• Colonized with resistant organisms
• Prophylactic quinolone
• Local susceptibilities
• Allergies
• Antimicrobial choices
  – Antipseudomonal activity
  – Bactericidal nature

• Monotherapy preferred
  – Cefepime
  – Imipenem/cilastin
  – Meropenem
  – Piperacillin/tazobactam
  – Cefazidime
• Combination therapy
  – For suspected resistance*
• Oral (low risk)
  – Ciprofloxacin and amoxicillin/clavulanate
  – Moxifloxacin


Clinical Case

• Empiric antibiotics ordered
  – Vancomycin 1 g IV every 12 hours
  – Piperacillin/Tazobactam 4.5 g IV every 6 hours

Should G-CSF be ordered for this patient?

IV = intravenously.
Adjunctive CSF with Antibiotics

- "CSFs should not be routinely used as adjunctive therapy with antibiotics" – ASCO Guidelines 2015
- They can be considered for patients at high risk of infection-associated complications or those who have prognostic factors predictive of poor clinical outcomes

Risk Factors for Poor Clinical Outcomes

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Clinical Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis syndrome</td>
<td>Aged &gt;65 years</td>
</tr>
<tr>
<td>Profound neutropenia (ANC &lt;100/mm³)</td>
<td>Neutropenia expected to be &gt;10 days</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Invasive fungal infection or other clinically documented infection</td>
</tr>
<tr>
<td>Hospitalized at time of fever</td>
<td>Prior episode of FN</td>
</tr>
</tbody>
</table>


Recent Systematic Analysis from Cochrane Library

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall mortality (n=1335)</td>
<td>0.74 (0.47-1.16; P=0.19)</td>
</tr>
<tr>
<td>Infection-related mortality (n=897)</td>
<td>0.75 (0.47-1.20; P=0.23)</td>
</tr>
<tr>
<td>Hospitalized for &gt;10 days (n=1087)</td>
<td>0.65 (0.44-0.95; P=0.03)</td>
</tr>
<tr>
<td>Duration of grade IV neutropenia (n=1135)</td>
<td>1.7 standard deviation below control</td>
</tr>
<tr>
<td>Time to recovery from fever</td>
<td>0.49 standard deviation below control</td>
</tr>
<tr>
<td>Time to withdrawal from antibiotics</td>
<td>1.5 standard deviation below control</td>
</tr>
</tbody>
</table>

Conclusions: No change in mortality, faster time to recovery, fewer patients in hospital for 5-10 days, fewer days of IV antibiotics, and shorter time to fever resolution

CI = confidence interval; IV = intravenous.

Patient Case

- Hospital course
  - After some discussion, G-CSF was added (300 mcg subcutaneously daily)
  - Afebrile after 24 hours of antibiotics
  - Cultures remained negative
  - ANC >1000 cells/µL on day 4, patient discharged home the next day
  - Antibiotics stopped at that time

- Planning cycle 2
  - Radiologic evaluation of FN showed tumor starting to respond to treatment
  - Continue with 3 more cycles of AC followed by 4 cycles of paclitaxel

Should we add G-CSF to cycle 2 of chemotherapy?

AC = doxorubicin/cyclophosphamide.
Secondary Prophylaxis

- Secondary prophylaxis: Starting CSF with cycle 2 or later and continuing throughout remaining schedule of a specific antineoplastic regimen due to an episode of neutropenic fever with the previous cycle of treatment.
- Consideration should be given to a dose reduction or delay in lieu of CSF support when clinically appropriate.
- Maintaining dose intensity with CSF is crucial in the setting of curative-intent chemotherapy.


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Secondary Prophylaxis

- Prior use of CSFs
- FN or dose-limiting neutropenic event
- Treatment regimen administered 1+ times

- No prior CSFs
- Consider chemotherapy dose reduction or change in treatment regimen

- No FN or dose-limiting neutropenic event
- Continue TX

- Desire to continue this regimen:
- Add CSF to prevent FN


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What Is Best for Our Case?
Key Question: Do CSFs Differ in Efficacy?

ASCO Guidelines addressed this question (clinical question 11)

Clinical interpretation:
Filgrastim, tbo-filgrastim, filgrastim-sndz, and pegfilgrastim are all effective in the reduction of the risk of FN. Factors such as convenience and cost may in some cases be dictated by the patient's treatment plan (eg, weekly chemotherapy).

What Is Best for Our Case?

Consider the Following Factors

• Relative efficacy of available agents
• Relative toxicity of available agents
• Cost implications
• Patient-specific factors (e.g., convenience)


What Do the Guidelines Say?

HSCT = hematopoietic stem cell transplantation; AML = acute myeloid leukemia.

Product | Indication(s)
--- | ---
Filgrastim | After myelotoxic chemotherapy, after autologous HSCT, and for peripheral blood progenitor cell mobilization
Filgrastim-sndz (biosimilar) | After myelotoxic chemotherapy, after autologous HSCT, and for peripheral blood progenitor cell mobilization
Intefilgrastim | After myelotoxic chemotherapy
Pegfilgrastim | After myelotoxic chemotherapy
Sargramostim | Peripheral blood progenitor cell mobilization; after autologous HSCT, after allogeneic bone marrow transplantation, for patients with AML

G-CSF vs Placebo

What Is the Difference between These 175 AA Sequences?

The name, cost, excipients, and indications. AA = amino acid.

Are tbo-Filgrastim and Filgrastim Interchangeable?

Neutropenic Fever Rates
- tbo-Filgrastim 12.1%
- Filgrastim (Eur) 12.9%
- Placebo 36.1%


Biosimilar Filgrastim-sndz

- As a biosimilar, randomized comparative trials were not performed
- However, results from a prospective trial compared with historic controls show equivalence

Results for the Primary Endpoint for Study EP06-302

<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>EP2006 (N=101)</th>
<th>Neupogen® (N=103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean DSN (SD) (days)</td>
<td>1.17 (1.11)</td>
<td>1.20 (1.02)</td>
</tr>
<tr>
<td>Neupogen® minus EP2006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DSN difference (days) (90% CI)</td>
<td>0.04</td>
<td>(-0.21, 0.28)</td>
</tr>
</tbody>
</table>

DSN = duration of severe neutropenia; SD = standard deviation.
G-CSF vs GM-CSF

- Not completely relevant for our case based on the indication and data
- Small studies show similar results, but large comparative trials in solid tumors are absent
  - Filgrastim, G-CSF
  - Escherichia coli derived
  - Dose 5 μg/kg/d
  - Target cells are late precursors to granulocytes
  - Sargramostim, GM-CSF
  - Yeast derived
  - Dose 250 μg/m²
  - Target cells are early precursors to monocytes and granulocytes

GM-CSF = granulocyte-macrophage colony stimulating factor.

Filgrastim and Pegfilgrastim Provide Comparable Neutrophil Recovery


Most common toxicity
- Treated with APAP or NSAID (evaluate kidney and plt)
- Similar between agents

APAP = paracetamol; NSAID = nonsteroidal anti-inflammatory drug; FDA = US Food and Drug Administration.
Convenience: Outpatient Chemotherapy

- Outpatient chemotherapy given weekly
  - Pegfilgrastim is not an option because of the long half-life
  - Filgrastim is best option
    - Started 1-3 days after chemotherapy
    - Given daily until ANC ≥ 2000-3000/μL
- Outpatient chemotherapy given every 14 or 21 days
  - Pegfilgrastim as a one-time injection is most convenient
  - 1 dose given 1-3 days after chemotherapy


Convenience: Inpatient Chemotherapy and Neutropenic Fever

- Inpatient chemotherapy
  - Equally convenient
  - When done for transplant patients, pegfilgrastim lacks data and indication (dosed as noted on previous slide)
- Inpatient neutropenic fever
  - Equally convenient
  - Pegfilgrastim lacks data and indication (dosed as noted on previous slide)


How Does the Cost Compare?

<table>
<thead>
<tr>
<th>Agent</th>
<th>Payment Limit (CMS)</th>
<th>Payment Limit per Dose (300 mcg)</th>
<th>Payment Limit per 15-day Tx (300 mcg)</th>
<th>Payment Limit per Dose (480 mcg)</th>
<th>Payment Limit per 15-day Tx (480 mcg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filgrastim</td>
<td>$1.001/1 mcg</td>
<td>$300.30</td>
<td>$3003</td>
<td>$480.48</td>
<td>$4804.80</td>
</tr>
<tr>
<td>ibo-Filgrastim</td>
<td>$0.706/1 mcg</td>
<td>$211.80</td>
<td>$2118</td>
<td>$338.88</td>
<td>$3388.80</td>
</tr>
<tr>
<td>Filgrastim-sndz</td>
<td>$0.783/1 mcg</td>
<td>$234.90</td>
<td>$2349</td>
<td>$375.84</td>
<td>$3758.40</td>
</tr>
<tr>
<td>Pegfilgrastim</td>
<td>$41,17.23/6 mg</td>
<td>$4117.23</td>
<td>$4117.23</td>
<td>$4117.23</td>
<td>$4117.23</td>
</tr>
</tbody>
</table>

*Does not include standard 6% mark-up
CMS = Centers for Medicare & Medicaid Services; Pt = patient; Tx = treatment.
### Budget Impact Analysis: Clinical Administration (Payer Perspective)

<table>
<thead>
<tr>
<th>Short-Acting G-CSF Product</th>
<th>Current Scenario Total Annual Plan Cost (PMPM/PMPY)</th>
<th>Future Scenario Total Annual Plan Cost (PMPM/PMPY)</th>
<th>Difference in Total Annual Plan Cost (PMPM/PMPY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>tbo-filgrastim</td>
<td>$48,131,940</td>
<td>$54,969,724</td>
<td>$6,837,784</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>$124,073,138</td>
<td>$111,586,094</td>
<td>$-12,487,044</td>
</tr>
<tr>
<td>Filgrastim-sndz</td>
<td>$4,946,840</td>
<td>$8,674,628</td>
<td>$3,727,788</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>$177,151,918</strong></td>
<td><strong>$175,230,446</strong></td>
<td><strong>-$1,921,473</strong></td>
</tr>
</tbody>
</table>

Data suggest that higher utilization of healthcare–provider-administered tbo-filgrastim and filgrastim-sndz may provide a more affordable option for payers.

PMPM = per member per month; PMPY = per member per year.


### Budget Impact Analysis: Patient Administration (Payer Perspective)

<table>
<thead>
<tr>
<th>Short-Acting G-CSF Product</th>
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<th>Future Scenario Total Annual Plan Cost (PMPM/PMPY)</th>
<th>Difference in Total Annual Plan Cost (PMPM/PMPY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>tbo-filgrastim</td>
<td>$2,311,211</td>
<td>$4,703,546</td>
<td>$2,392,335</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>$46,037,202</td>
<td>$42,260,349</td>
<td>$-3,776,853</td>
</tr>
<tr>
<td>Filgrastim-sndz</td>
<td>$4,949,804</td>
<td>$5,864,937</td>
<td>$915,133</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>$53,298,217</strong></td>
<td><strong>$52,828,832</strong></td>
<td><strong>-$469,385</strong></td>
</tr>
</tbody>
</table>

Data suggest that increasing utilization of tbo-filgrastim and filgrastim-sndz in situations where patients self-administer short-acting G-CSFs may provide a more affordable option for payers.

PMPM = per member per month; PMPY = per member per year.


### CSF Primary Prophylaxis

- Primary prophylaxis: Start CSF with cycle 1 and continue throughout the entire schedule of a specific antineoplastic regimen
- Reserve for patients receiving chemotherapy with >20% or higher risk of FN
- Use in patients receiving “dose-dense” chemotherapy (eg, lymph node positive breast cancer with adjuvant chemotherapy)
- Consideration should be given to alternate, equally effective, and safe chemotherapeutic regimens not requiring CSF support

Regimens with High Rates of FN

<table>
<thead>
<tr>
<th>Disease</th>
<th>Regimen</th>
<th>Rate of FN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
<td>Carboplatin/paclitaxel</td>
<td>21%</td>
</tr>
<tr>
<td></td>
<td>Dose-dense MVAC (with G-CSF support)</td>
<td>NR</td>
</tr>
<tr>
<td>Breast</td>
<td>Doxorubicin/docetaxel</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td>Doxorubicin/docetaxel/cyclophosphamide</td>
<td>24%-34%</td>
</tr>
<tr>
<td></td>
<td>Docetaxel</td>
<td>21%</td>
</tr>
<tr>
<td>Germ Cell Tumor</td>
<td>Vinblastine, ifosfamide, cisplatin</td>
<td>71%</td>
</tr>
<tr>
<td>Lung</td>
<td>Cyclophosphamide/doxorubicin/docetaxine</td>
<td>26%</td>
</tr>
<tr>
<td></td>
<td>Topotecan</td>
<td>28%</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Etoposide/methylprednisolide/cisplatin/ctarabine</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone/cisplatin/ctarabine</td>
<td>48%</td>
</tr>
</tbody>
</table>

MVAC = methotrexate, vinblastine, doxorubicin, cisplatin; NR = no risk.

Determining Primary Use (with Cycle 1)

<table>
<thead>
<tr>
<th>Risk of FN</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk &gt;20%</td>
<td>CSF</td>
</tr>
<tr>
<td>Intermediate risk 10%-20%</td>
<td>Consider CSF</td>
</tr>
<tr>
<td>Low risk &lt;10%</td>
<td>No CSF</td>
</tr>
</tbody>
</table>

• Regimen-related risk
• Personal risk
• Cost of hospitalization for patient with FN


Regimen Rates of FN

• The risk of FN from doxorubicin/cyclophosphamide without a CSF is intermediate (10%-20%)
• The use of a CSF should be considered based on individual risk factors

Patient Risk Factors That Increase the Risk of FN

**Risk factors**
- Age ≥65 years
- Advanced disease
- Previous chemotherapy or radiation therapy
- Pre-existing neutropenia or bone marrow involvement with tumor infection
- Open wounds or recent surgery
- Poor performance status or poor nutritional status
- Poor renal function
- Liver dysfunction, most notably elevated serum bilirubin levels
- Cardiovascular disease
- Multiple comorbid conditions
- Human immunodeficiency virus infection


Clinical Case Summary

- No indication to start G-CSF primary prophylaxis
- Secondary G-CSF prophylaxis is key in this situation
  - Curative intent
  - Standard regimen
  - Early indication of response
- Once patient developed FN, she was treated with antibiotics, considering prior resistant organism
- G-CSF was added to antibiotics due to early severe neutropenia and the desire to keep her out of the hospital and on track with chemotherapy

Final Thoughts

- For myelotoxicity filgrastim, pegfilgrastim, filgrastim-sndz, and ibo-filgrastim, all decrease risk of FN, duration of severe neutropenia, and rate of hospitalization
- Guideline-based prescribing for CSFs in the clinical setting of primary and secondary prophylaxis lowers complications secondary to chemotherapy-associated neutropenia
- Choosing an agent is based on convenience, cost, and treatment plan
  - Budget impact models may help assess costs that can be individualized to an institution
  - Relevant treatment costs include CSF pricing, hospital day, and hospitalization duration