Evaluation of G-CSF Use in a Single Institution and Development of Pocket Reference for Primary Prophylaxis of Chemotherapy-Induced Febrile Neutropenia

Taylor W. Butler, PharmD; J. Aubrey Waddell, PharmD; Brad J. Crane, PharmD; Amy M. Porter, PharmD

Background: Granulocyte colony-stimulating factors (G-CSFs) are often prescribed as primary prophylaxis for patients with chemotherapy-induced febrile neutropenia (CIFN). Clinical controversy surrounds the appropriate use of G-CSFs. The American Society of Clinical Oncology (ASCO) recommends avoiding these medications in patients with a low risk for CIFN. Optimizing the use of G-CSFs was recently identified as a top method for reducing cost in patients with cancer. The extent of unnecessary use is unknown at many cancer institutions and is not well studied. Many difficulties present with identifying patients at a low risk for CIFN, and there are limited published studies available to help guide prescribing patterns.

Objectives: To evaluate the use of G-CSFs for adherence to the ASCO guidelines at Blount Memorial Hospital, as well as to create a reference guide for the future assessment of the risk for CIFN.

Methods: A retrospective chart review was conducted for each patient who had received chemotherapy at Blount Memorial Hospital between December 2010 and December 2012. A total of 256 patients were reviewed for the risk of CIFN, which included a review of the patient’s history and the chemotherapy regimen administered. The type of G-CSF and the number of doses used were collected and extrapolated using average wholesale price to determine potential cost-savings. PubMed and MEDLINE were searched for relevant clinical trials. Primary literature was reviewed to identify articles that reported a rate of febrile neutropenia for each regimen administered among the participating patients. These rates were compiled into a pocket reference to be distributed to prescribers at the conclusion of this review.

Results: The results of this evaluation showed that prescribers were compliant with the ASCO guidelines in approximately 69% of the cases. Based on these findings, this institution could save more than $600,000 during the study period if G-CSFs were only administered in patients with a risk of \( \geq 20\% \) for developing CIFN. Furthermore, the rates of febrile neutropenia were discovered in the primary literature for 100 different chemotherapy regimens and were organized into a pocket reference.

Conclusion: This analysis of a single community institution shows that patients with cancer undergoing chemotherapy are inconsistently evaluated for CIFN and are often prescribed these medications against ASCO guidelines. With the growing costs and the negative adverse events associated with these medications, prescribers need a readily available reference source to enhance their ability to evaluate patients for CIFN and manage it appropriately. Furthermore, the rates of febrile neutropenia in patients with cancer need to be compiled and provided to frequent prescribers to assist them with patient evaluation for CIFN risk until further research is available. More research is needed in this area to improve patient evaluation for this risk.

Disclosures are at end of text

Vol 4, No 1 | March 2014 | www.JHOPonline.com | Journal of Hematology Oncology Pharmacy
Chemotherapy-induced febrile neutropenia (CIFN) is a life-threatening, costly complication that may develop in patients with cancer after receiving myelosuppressive chemotherapy. In 1991, filgrastim (Neupogen) was approved for the treatment of patients with CIFN, because it stimulates the production of neutrophils, which potentially treats and prevents febrile neutropenia. Filgrastim, pegfilgrastim (Neulasta), and sargramostim (Leukine) are classified as granulocyte colony-stimulating factors (G-CSFs). A 2005 study of the use of pegfilgrastim showed that the G-CSFs were effective in the prevention of febrile neutropenia. Despite this finding, the determination of which chemotherapy regimens require primary prophylaxis for CIFN with G-CSFs is still controversial.

In 2012, the American Society of Clinical Oncology (ASCO) identified the appropriate use of G-CSFs as 1 of the top 5 recommendations to reduce expenditures for patients with cancer. In addition to a potential financial detriment, inappropriate prescribing of these medications may also lead to unnecessary adverse reactions, most often injection-site reactions, flu-like symptoms, and bone pain. The ASCO guidelines define inappropriate use as administering these medications to patients with a low, <20% risk for developing CIFN.

In this current study, we evaluated the use of G-CSFs and attempted to develop a reference guide to provide prescribers relevant CIFN rates associated with specific medications, in the hopes of optimizing the use of these medications at our institution.

Methods
We performed a retrospective chart review for all patients who received chemotherapy at our community institution, which has 300 inpatient beds and a 20-chair outpatient infusion clinic. The data were collected from December 1, 2010, to December 31, 2012 (ie, 25 months). No exclusion criteria were included in this review. Data collection included the type of malignancy, the chemotherapy regimen used, and the administration of G-CSFs. Patients’ charts were also reviewed to identify patients with a documented episode of febrile neutropenia.

The primary literature was extensively reviewed to determine the rates of CIFN in patients with cancer. PubMed and Ovid MEDLINE were the search engines used to locate the relevant clinical trials. The search was limited to phase 1, phase 2, or phase 3 clinical trials and included the chemotherapy drugs used in each of the regimens. Approximately 300 relevant articles and almost 200 regimens were found in our search of the literature. The trials found in this search were included in the analysis when documented rates of febrile neutropenia, neutropenic fever, or neutropenic sepsis were listed.

The rates of primary prophylaxis of CIFN in each trial and the related regimens were compiled into a pocket guide for clinician reference. The highest rate of febrile neutropenia in each trial would determine a patient’s risk level. Each chemotherapy regimen, the rate of febrile neutropenia, and the reference for every clinical trial included in this evaluation were listed in the pocket guide. The data analysis was conducted in
the form of descriptive statistics using Microsoft Excel. Each chemotherapy regimen was evaluated using the ASCO guidelines, and the potential cost-savings were calculated based on average wholesale price and the elimination of unnecessary administrations of G-CSFs over the full study period.

Results

This evaluation included 256 patients who received 322 different chemotherapy regimens at our institution. The evaluation of the use of G-CSFs in these patients is described in Table 1. G-CSFs were administered after 140 (43.5%) of the 322 chemotherapy regimens. Only 77 (23.9%) regimens prescribed at our institution had a risk of ≥20% for developing CIFN. Of note, 25.5% of regimens administered were for hematologic malignancies (primarily acute myeloid leukemia and non-Hodgkin lymphoma) compared with 74.5% for solid tumors (primarily breast cancer and lung cancer). A total of 223 of the 322 (69.3%) regimens used at our institution were compliant with the ASCO guidelines with G-CSFs, and the other regimens were not compliant with the guidelines.

When G-CSFs were administered (N = 140), approximately 59 (42.1%) of the prescriptions were in compliance with the ASCO guidelines (Figure). In addition, 18 of the 77 (23.4%) high-risk regimens were not followed with prophylaxis for febrile neutropenia.

Of note, 6 chemotherapy regimens did not have published articles that reported the data for the rate of CIFN. Table 2 shows how these 6 cases were evaluated in our analysis for the risk of CIFN. Two regimens were administered G-CSFs for secondary prophylaxis of CIFN.

Based on these results, if all prescribers at our institution avoided the administration of G-CSFs in patients with a <20% risk for CIFN, more than $600,000 would have been saved during this study period.

The completed reference guide based on our review of the literature contained CIFN rates for 100 different chemotherapy regimens. Only 24 regimens showed a risk of >20% for developing this complication.

Discussion

The use of G-CSFs in our institution suggests that the prescribing of these medications is not always in compliance with current ASCO guidelines. Furthermore, there is some disagreement regarding the definition of low risk for CIFN between the ASCO guidelines and the NCCN recommendations.

Full compliance with the ASCO guidelines for G-CSFs use is not expected, because of a variety of factors, including treatment goals and patient comorbidities; however, it is concerning that in one representative (our) institution, 57.9% (81 of 140) of patients receiving these medications

<table>
<thead>
<tr>
<th>Characteristics of 322 chemotherapy regimens used at a single institution</th>
<th>Regimens used, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk for CIFN</td>
<td></td>
</tr>
<tr>
<td>≥20%</td>
<td>77 (23.9)</td>
</tr>
<tr>
<td>&lt;20%</td>
<td>245 (76.1)</td>
</tr>
<tr>
<td>G-CSF administered</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>140 (43.5)</td>
</tr>
<tr>
<td>No</td>
<td>182 (56.5)</td>
</tr>
<tr>
<td>Compliant with ASCO guidelines</td>
<td></td>
</tr>
<tr>
<td>G-CSF used in patients with ≥20% of CIFN risk</td>
<td>223 (69.3)</td>
</tr>
<tr>
<td>G-CSF not used in patients with &lt;20% of CIFN risk</td>
<td>59</td>
</tr>
<tr>
<td>Noncompliant with ASCO guidelines</td>
<td></td>
</tr>
<tr>
<td>G-CSF used in patients with &lt;20% of CIFN risk</td>
<td>99 (30.7)</td>
</tr>
<tr>
<td>G-CSF not used in patients with ≥20% of CIFN risk</td>
<td>81</td>
</tr>
</tbody>
</table>

ASCO indicates American Society of Clinical Oncology; CIFN, chemotherapy-induced febrile neutropenia; G-CSF, granulocyte colony-stimulating factor.

Table 1: Evaluation of G-CSF Use for 322 Chemotherapy Regimens Used in 256 Patients

Figure G-CSF Administered in 140 Patients with Cancer

CIFN indicates chemotherapy-induced febrile neutropenia; G-CSF, granulocyte colony-stimulating factor.
had a risk of <20% for CIFN. Furthermore, 39 of these 81 (48.1%) patients who received G-CSFs against the ASCO recommendations had a <10% risk for febrile neutropenia. By comparison, Fishman and colleagues reported that 52 of 245 (21%) total units of pegfilgrastim were administered for patients at low risk for febrile neutropenia.

The most common regimens administered against the ASCO guidelines at Blount Memorial Hospital were azacitidine and eribulin.

Noncompliance may also be explained by other factors. The rates of febrile neutropenia can be difficult to locate, including the challenges of gaining access to clinical trials or finding trials that actually studied or reported CIFN. Regimens included in this review required several hours to ascertain a clear clinical picture of whether G-CSFs were indicated for CIFN.

The G-CSF medications were not available until the early 1990s, so many clinical trials before that time did not place the same emphasis on febrile neutropenia rates after chemotherapy. Rates of neutropenia or leukopenia are usually well documented in clinical trials today, but they can potentially lead to a detrimental clinical impact (ie, infection, death). Also, there is not always a correlation between neutropenia and neutropenic fever for every chemotherapy regimen.

A more in-depth risk assessment tool is needed to ensure the optimal use of G-CSFs. The Multinational Association of Supportive Care in Cancer provides a risk assessment calculator for febrile neutropenia, but it is primarily used in practice to determine if a patient can be treated with outpatient antibiotics. It is unknown whether this tool can help clinicians with the prescribing of G-CSFs for primary prophylaxis.

These medications are costly, and represent an additional injection, as well as the potential for adverse events for patients with cancer; it is therefore important to correctly evaluate the need before administering them.

Table 3 provides the reference guide created for this study and lists the rates of CIFN associated with chemotherapy regimens at our institution based on clinical trial results. Providing prescribers with such a guide from institutional-specific chemotherapy regimens may aid in the evaluation of need, and can potentially eliminate the risk of not prescribing these medications when indicated, as well as decreasing the rate of unnecessary administrations of G-CSFs at institutions such as ours.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>The Rationale for 6 Chemotherapy Regimens Administered without Supporting Data in the Literature&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regimen</td>
<td>Graded</td>
</tr>
<tr>
<td>6-thioguanine + cytarabine + idarubicin</td>
<td>High</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Low</td>
</tr>
<tr>
<td>Idarubicin + all-trans retinoic acid</td>
<td>High</td>
</tr>
<tr>
<td>Idarubicin + cytarabine + vincristine + methotrexate</td>
<td>High</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>Low</td>
</tr>
<tr>
<td>Cyclophosphamide + rituximab</td>
<td>Low</td>
</tr>
</tbody>
</table>

<sup>a</sup>These regimens did not have published data for their CIFN risk; references cited explain the rationale for assessing a CIFN risk for each regimen.

CIFN indicates chemotherapy-induced febrile neutropenia.
Table 3  Example Pocket Reference Created Based on Chemotherapy Regimens Used in a Single Institution

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Rate of febrile neutropenia, %</th>
<th>Regimen</th>
<th>Rate of febrile neutropenia, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABVD every 3 wks</td>
<td>3-918,19</td>
<td>Cyclophosphamide 600 mg/m² + doxorubicin</td>
<td>217</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60 mg/m² every 3 wks</td>
<td></td>
</tr>
<tr>
<td>Alectuzumab 30 mg 3 times weekly</td>
<td>0-1420,22</td>
<td>Cyclophosphamide 187.5-400 mg/m² daily + doxorubicin 12.5 mg/m² daily + etoposide 60-90 mg/m² daily continuous infusions (days 1-4)</td>
<td>Standard practice26,27</td>
</tr>
<tr>
<td>Azacitidine 75 mg/m² (days 1-7) every 4 wks</td>
<td>823</td>
<td>Cyclophosphamide 600 mg/m² + epirubicin 60-90 mg/m² + fluorouracil 600 mg/m² every 3 wks</td>
<td>1-1028,29</td>
</tr>
<tr>
<td>BCG live every wk</td>
<td>&lt;124</td>
<td>Cyclophosphamide 600 mg/m² + epirubicin 60-90 mg/m² every 3 wks + trastuzumab</td>
<td>3-100</td>
</tr>
<tr>
<td>Bevacizumab 5-15 mg/kg every 2 wks</td>
<td>&lt;123</td>
<td>Cyclophosphamide 600 mg/m² + nab-paclitaxel 100 mg/m² (days 1, 8, 15) + trastuzumab 6 mg/kg every 21 days</td>
<td>217</td>
</tr>
</tbody>
</table>

ABVD indicates Adriamycin, bleomycin, vinblastine, dacarbazine; BCG, Bacillus Calmette-Guérin.

Limitations
A confounding factor in the current analysis is that previously documented cases of febrile neutropenia were not well recorded at our institution. We found 2 documented cases of previous febrile neutropenia in our review, and we hypothesize that more than 2 patients developed febrile neutropenia and required secondary prophylaxis with G-CSFs. Patients could also possibly have received G-CSFs at another site.

In addition, a weakness in the evaluations of risk for CIFN is that there are few available data on how to evaluate additional factors that may potentially affect the patient’s risk for CIFN. This leaves room for interpretation that may vary between prescribers.

Conclusion
Improving the optimal use of G-CSFs will require future research, including the evaluation of confounding factors associated with the evaluation of CIFN. A risk assessment tool needs to be developed and evaluated in a clinical trial to determine the exact impact of the many variables associated with febrile neutropenia, including the patient’s age and potential for bone marrow compromise. Until this research is completed, the first step is to increase awareness of the risk for CIFN with each regimen. Providing institution-specific reference guides may immediately help improve compliance rates, with the primary focus not only on limiting the inappropriate administrations, but also on making sure patients get these medications when indicated. Our institution will be reevaluated in the future to determine if the pocket reference improves compliance with ASCO guidelines and reduces the expenditure associated with the inappropriate use of G-CSFs.

Author Disclosure Statement
Dr Crane is Principal Investigator and Study Site Coordinator for the CAPTURE study for Cerexa, a subsidiary of Forest Pharmaceuticals. Dr Butler, Dr Waddell, and Dr Porter have reported no conflicts of interest.

References
Principles in Value and Market Access

An educational session for product managers, reimbursement specialists, account managers, and marketers focusing on access, reimbursement, proving product value, and international markets.

May 6, 2014
Loews Hollywood Hotel
Los Angeles, CA

AGENDA

10:45am – 11:00am  Introductions and Opening Remarks
Grant Lawless, RPh, MD, FACP; Gary M. Owens, MD

11:00am – 11:40am  Changing Access and Payer Challenges in Oncology - Medicare and Commercial
Speaker TBD

11:40am – 12:20pm  Proving the Value for Oncology Therapy Using Comparative Effectiveness Research
Dan Malone, PhD, Professor, University of Arizona College of Pharmacy

12:20pm – 1:30pm Lunch

1:30pm – 2:10pm  Methods and Tools for Optimal Reimbursement
Sasha Richardson, BSC, PT, MBA, Vice President, GfK Bridgehead

2:10pm – 2:50pm  Impact of Healthcare Reform, Affordable Care Act, and Accountable
Care Organizations on the Coverage of Cancer Treatments
Speaker TBD

2:50pm – 3:30pm Impact of New Risk Models on Traditional Pharmaceutical Relationships
Ken Schaecher, MD, FACP, CPC, Medical Director, SelectHealth

3:30pm – 4:00pm Break

4:00pm – 4:40pm Using Competitive Intelligence to Maintain Coverage and Access
Cyrus Arman, MS, PhD, Principal & Head of West Coast Operations, Deallus Consulting

4:40pm – 5:20pm Panel Discussion - Will improvements in clinical outcomes and efficacy come from
new products or a more thoughtful use of existing products using new adaptations?
Cyrus Arman, MS, PhD, Principal & Head of West Coast Operations, Deallus Consulting
Sasha Richardson, BSC, PT, MBA, Vice President, GfK Bridgehead
Andrew Stainthorpe, Executive Director, National Institute for Health and Clinical
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