neutropenia is a common dose-limiting toxicity of myelosuppressive chemotherapy and exposes patients to life-threatening infections and treatment delays. Febrile neutropenia, a concerning complication of chemotherapy, is defined as neutropenia associated with an oral temperature of more than 38.5°C or 2 consecutive readings of more than 38.0°C for 2 hours and an absolute neutrophil count of <0.5 × 10^9/L, or a count that is expected to decrease to less than 0.5 × 10^9/L within 48 hours. Despite advances in therapy, febrile neutropenia remains a major cause of morbidity, mortality, dose reductions, treatment delays, increased hospitalizations, extended hospital length of stay, and increased treatment costs. Kuderer and colleagues estimated a 9.5% (95% confidence interval, 9.5%-9.8%) direct mortality

**Comparing Granulocyte Colony-Stimulating Factors Prescribing Practices versus Guideline Recommendations in a Large Community Cancer Center**

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**BACKGROUND:** Despite established guidelines for the use of granulocyte colony-stimulating factors (G-CSFs) in the prevention of febrile neutropenia, inappropriate prescribing practices have been reported.

**OBJECTIVES:** To evaluate the use of G-CSFs in a large community cancer center in relation to the National Comprehensive Cancer Network (NCCN) recommendations, and to implement a pharmacist reference to ensure optimal G-CSF management and decrease healthcare spending.

**METHODS:** We conducted a retrospective chart review to evaluate the administration of G-CSFs in 2014 in a large community cancer center. Data collected included the type of malignancy, chemotherapy regimens, and patient comorbidities. Recommendations from the NCCN and from the American Society of Clinical Oncology and the published literature regarding regimens associated with febrile neutropenia were used to determine appropriate therapy. Adults who had a diagnosis of cancer and received G-CSFs as prophylaxis for febrile neutropenia were included in this analysis. Patients who received G-CSF therapy for mobilization were excluded from this analysis.

**RESULTS:** A total of 72 patient encounters associated with filgrastim therapy and 1439 patient encounters with pegfilgrastim therapy were analyzed. The results demonstrated that 47.22% and 8.2%, respectively, of G-CSF administrations did not have an indication supported by guideline recommendations for administering filgrastim and pegfilgrastim as prophylaxis for febrile neutropenia. In addition, this evaluation helped to identify a potential saving of more than $600,000 annually. In all, 4.66% of pegfilgrastim treatment was administered on the same day as chemotherapy administration, despite guideline recommendations for a 24- to 72-hour wait period between the administrations of chemotherapy and G-CSF.

**CONCLUSION:** The use of G-CSFs at this large institution suggests that the prescribing of these medications is not always in adherence with the current NCCN guidelines. Our analysis helped to implement a systemwide pharmacist reference in collaboration with the medical oncologists in setting criteria to aid in the management of G-CSF therapy and provide optimal patient care.

**KEY WORDS:** community cancer center, febrile neutropenia, filgrastim, G-CSF therapy, granulocyte colony-stimulating factor, pegfilgrastim, prescribing practices

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risk for patients with cancer who were hospitalized with febrile neutropenia. Suboptimal chemotherapy treatment may affect patient outcomes and the overall efficacy of cancer management. Other considerations related to complications of febrile neutropenia include decreased quality of life and the use of broad-spectrum antibiotics.

Granulocyte colony-stimulating factors (G-CSFs), which were first approved in 1991, are effective at reducing the risk for and duration of chemotherapy-induced febrile neutropenia, by stimulating the production and maturation of neutrophils.

Guideline recommendations for the prevention and/or treatment of patients with febrile neutropenia have been published by the National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), and the Infectious Diseases Society of America (IDSA).

The ASCO and NCCN guidelines recommend primary prophylaxis with G-CSFs for patients at high risk for febrile neutropenia (ASCO, ≥20% risk; NCCN, >20% risk), and therapy is a consideration for certain patients with an intermediate risk (10%-20%) for febrile neutropenia. These guidelines also recommend that G-CSFs be administered 24 to 72 hours after chemotherapy. Secondary prophylaxis is recommended if febrile neutropenia or dose-limiting neutropenia have occurred with previous chemotherapy cycles.

In addition, the IDSA and the ESMO guidelines support the recommendations made by NCCN. The IDSA guidelines focus heavily on the treatment of febrile neutropenia with antibiotic therapy. The ASCO guidelines support the use of G-CSFs as primary prophylaxis in patients at high risk for a febrile neutropenic episode based on age, medical history, disease characteristics, and the regimen’s myelotoxic potential. The ASCO guidelines further advise against the use of G-CSFs in patients who have a less than 20% chance of neutropenic complications.

Despite the established clinical guidelines and approved indications by the US Food and Drug Administration, several factors play a role in the utilization of G-CSFs (ie, provider preference, care plan designs, inpatient and outpatient setting, the presence of adjuvant treatment, or metastatic disease), and physician surveys indicated prescribing patterns that lack evidence-based support.

The purpose of this retrospective analysis is to assess the overall use of growth factors within a large community cancer center. We evaluated the use of these agents for primary versus secondary prophylaxis (when prophylaxis was used with appropriate regimens) and the institution’s compliance with guideline recommendations. Information from this analysis was used as a basis for the development and implementation of a pharmacist reference to standardized myeloid growth factor use potentially to reduce cost. Before implementing this pharmacist reference, pharmacists played a limited role in the management of G-CSF therapy.

Methods

Our study was a single-site, retrospective health system chart review. The study was granted Institutional Review Board–exempt status, because it was a quality improvement project. The health system of the analysis consists of an inpatient oncology unit, 5 satellite clinics, and 3 outreach locations.

Adult patients aged ≥18 years were included if they had a cancer diagnosis and received prophylactic G-CSF support for the prevention of febrile neutropenia. This analysis excluded pediatric patients, patients receiving G-CSFs for stem-cell mobilization, and patients with nononcologic neutropenia. Patients who received therapy between January 2014 and December 2014, when filgrastim and pegfilgrastim were the only G-CSF agents on the hospital’s formulary, were included in the analysis. A charge report was generated from the pharmacy system that provided all the filgrastim and pegfilgrastim doses administered during this designated time frame (from January to December 2014). Manual chart reviews were conducted on patients who met the inclusion criteria to determine the appropriateness of prophylactic therapy.

The data were analyzed using descriptive statistics. Each patient was evaluated for appropriate use of primary prophylaxis if they met 1 of the following 3 criteria: (1) receiving G-CSF prophylaxis postchemotherapy as supported by the NCCN guidelines, with a >20% risk for febrile neutropenia; (2) receiving G-CSF prophylaxis postchemotherapy, as supported by at least 1 published study indicating a >20% risk for febrile neutropenia; or (3) receiving G-CSF prophylaxis postchemotherapy, as supported by the NCCN guidelines, with a 10% to 20% risk for febrile neutropenia associated with comorbidities placing the patient at an increased risk.

Secondary prophylaxis was deemed appropriate if the patient had any previously documented febrile neutropenia episode after receiving any cycle of chemotherapy. G-CSFs that were prescribed for self-administration were categorized as appropriate if the patient met the primary or secondary prophylaxis criteria, but patient compliance assessment was not feasible.

In addition, the timing of the dose administration was analyzed to ensure that patients received G-CSF therapy within 24 to 72 hours postchemotherapy, as is
recommended in the NCCN guidelines. We used our clinical judgment to determine the appropriateness of the timing of the G-CSF administration.

Patients who received a G-CSF on the same day as a fluorouracil infusion device removal were counted as appropriate; we believed that this administration was acceptable, considering the short half-life of the drug. Patients who did not meet the above criteria were classified as receiving G-CSF therapy inappropriately. Of note, our primary intent was to determine the total percentage of overutilization of G-CSF prophylaxis; therefore, the primary and secondary prophylaxis results are represented cumulatively in this study.

The data collected and keyed for analysis included demographics, including medical record number, initials, age, sex, weight, underlying diagnosis, tumor type, comorbidities, and physician name; laboratory testing results, including white blood cell count (at baseline, nadir, and before each cycle) and absolute neutrophil count (at baseline, nadir, and before each cycle); temperature, if febrile neutropenia; treatment, including chemotherapy regimen, treatment intent, G-CSF agent used, number of treatment days, number of doses administered, primary or secondary prophylaxis, inpatient or outpatient care, current neutropenic status, antibiotics if needed, concurrent radiation, timing of treatment, the use of care plans, cost, and the appropriateness of therapy; and comorbidities, including age ≥65 years, poor performance status, poor nutritional status, previous history of febrile neutropenia, preexisting neutropenia or lymphocytopenia, open wounds or recent surgery, active infection, low body surface area or body mass index, liver or renal dysfunction (bilirubin >2 mg/dL; creatinine clearance <50 mL/min), bone marrow involvement, advanced cancer, serum albumin <3.5 g/dL, low baseline hemoglobin, elevated lactate dehydrogenase, previous chemotherapy, or radiation therapy.

**Results**

This analysis screened 537 patients to determine their study participation eligibility. Of these patients, 476 patients—70 patients in the filgrastim arm and 406 in the pegfilgrastim arm—met the inclusion criteria and received G-CSF therapy. The Table lists patients’ demographics and the intent for prophylaxis. In all, 23 patients who received therapy for mobilization, 6 pediatric patients, and 32 patients with nononcologic neutropenia were excluded from the analysis.

We evaluated G-CSF utilization based on encounters from administration series. Administration series was defined as the period in which patients received G-CSFs for prophylaxis between chemotherapy cycles. A dose of pegfilgrastim resulted in a single encounter, and another encounter was a consecutive series of filgrastim administrations after a chemotherapy cycle. The 70 patients included in the filgrastim arm had a total of 72 encounters, because 2 patients received a G-CSF after 2 separate cycles of chemotherapy. The 406 patients who received pegfilgrastim had a total of 1439 administrations.

Based on the NCCN guideline recommendations and evidence from any study showing a >20% risk for febrile neutropenia, 47% (N = 34) of the filgrastim administrations did not meet the >20% risk for febrile neutropenia, and the patients in the filgrastim arm did not have comorbidities that placed them at an increased risk for febrile neutropenia with regimens that had a 10% to 20% risk for febrile neutropenia (Figure 1).

In all, 56% of these patients had breast cancer and were receiving weekly paclitaxel 80 mg/m², a regimen that does not typically require G-CSF support. A total of 4 medical oncologists contributed to these prescribed orders; of these prescribed orders, 52.3% of the doses were from a single prescriber. In addition, the results in the filgrastim arm showed that 31.94% (N = 23) of filgrastim administrations were >72 hours postchemotherapy, and 15.28% (N = 11) were administered on the same day as chemotherapy.

In the pegfilgrastim group, only 8.2% (N = 118) of all encounters did not meet the criterion of >20% risk for febrile neutropenia as supported by the NCCN guidelines and the published literature, and patients did not have comorbidities that increased their risk for febrile neutropenia (Figure 2).
The pegfilgrastim group was largely composed of patients with lymphoma (N = 39) and colorectal cancer (N = 22). Patients with lymphoma were receiving the combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (ie, R-CHOP) in a 21-day regimen, and patients with colorectal cancer were receiving the combination of fluorouracil, oxaliplatin, leucovorin (ie, FOLFOX), or with irinotecan (ie, FOLFIRINOX). A single provider prescribed 28.2% and 64.4% of pegfilgrastim doses postchemotherapy for lymphoma and colorectal cancer, respectively. Furthermore, the pegfilgrastim results demonstrated that 4.66% (N = 67) of administrations were on the same day as chemotherapy.

For a small subset (<2%) of patients in the filgrastim arm only, we noticed inconsistent daily administrations of the G-CSFs. This led us to investigate why a single dose of G-CSF was ordered in the clinic. We discovered that those patients were prescribed the remaining injections to be self-administered at home. We were not able to assess if these patients were adherent to their medication regimen.

Based on our findings, the use of filgrastim and/or pegfilgrastim contrary to current guideline recommendations contributed to more than $600,000 in healthcare expenditures in 2014. Although most of the inappropriate use of G-CSFs was linked to filgrastim, pegfilgrastim contributed more heavily to the healthcare expenditures, because of its significantly higher cost. In most situations, the inappropriate use of filgrastim was limited to only 2 to 3 doses on average; therefore, at $350 to $580 per dose, filgrastim contributed less to the healthcare expenditures than pegfilgrastim, which cost approximately $6000 per dose.17,18

### Discussion

Several published studies report inappropriate use of G-CSFs among institutions and providers,11,19-23 which support our findings. Wright and colleagues analyzed 25,231 patients who received treatment for febrile neutropenia over a 10-year period to assess guideline-based management.19 Of these patients, 62.1% were low-risk and 65.9% were high-risk patients and received G-CSF for the treatment of febrile neutropenia.19 Because of a large variation in practice patterns, this analysis recom-
mended the use of systemwide protocols, formalized guidelines, or electronic medical record alerts to improve utilization, outcomes, and expenditures.\(^{19}\)

In addition, a survey of more than 1200 oncologists by Freifeld and colleagues demonstrated that 28% of the physicians prescribed G-CSF prophylactically in patients at low risk for febrile neutropenia and 48% prescribed G-CSF as an adjunct to antibiotics for the treatment of febrile neutropenia.\(^{24}\) In their 2013 review article, Waters and colleagues have also reported the overutilization of pegfilgrastim in up to 46% of patients receiving chemotherapy with <20% risk for febrile neutropenia.\(^{23}\)

By comparison, the inappropriate use of G-CSFs is less prevalent in our community cancer center than in the NCCN guidelines.\(^{10}\) However, with room for decreasing expenditures, our analysis provides information to aid in the implementation of pathways that use clinical pharmacists to improve compliance with guidelines. Ignoffo and colleagues demonstrated the impact that board-certified oncology pharmacists have on patient visits and the value of their addition to the healthcare team.\(^{25}\) Although oncology pharmacists may substantially reduce the shortfall of providers who are needed for oncology patient visits, their expertise can aid in optimal pharmacotherapy management through collaborative practices.

As previously noted, factors such as physician training and experience, a lack of standardized protocols, and hospital practice settings can affect therapy selection.\(^{3,26-28}\) Although deviation from practice guidelines may be warranted in specific cases, and complete guideline compliance is improbable, there is clear potential for improving the use of febrile neutropenia therapy.

After presenting these data to the medical director and staff, we reached a consensus to create a pharmacist reference for the oncology pharmacists to use their abilities and ensure guideline compliance. The reference outlines several key assessments for the oncology pharmacist to aid in determining the need for G-CSF support.

First, an extensive list of chemotherapeutic regimens and the incidence of febrile neutropenia was designed, by conducting extensive literature reviews, reviewing the NCCN guidelines, and collaborating with Butler and colleagues, who provided a pocket reference guide from their published works.\(^{29}\) This list will be used to compare each patient’s regimen with the risk for febrile neutropenia.

Second, the pharmacist reference defines the patient criteria, as mentioned above, that would place the patient at an increased risk for febrile neutropenia. The institutional pharmacist reference outlines opportune scenarios at which a board-certified oncology pharmacist should intervene if patients do not meet the criteria outlined and warrant a conversation with the medical team to determine if G-CSF therapy is appropriate.

Finally, the institution’s future direction will be to enroll in a Southwest Oncology Group clinical trial that is intended to evaluate prospectively a standing order intervention and to determine the effectiveness of G-CSF use as prophylaxis for patients who receive chemotherapy who are at intermediate risk for febrile neutropenia.\(^{20}\)

**Limitations**

Despite findings that are supported by current guidelines,\(^{10}\) this analysis has several limitations. Because of the method used for data collection, we were unable to analyze cohorts of patients who might have been candidates for G-CSF support but who did not receive therapy (ie, underutilization).

Also, our institution utilizes several data systems, as well as paper charts, which made data collection an intensive manual process. Errors in the medical record system and undocumented cases of febrile neutropenia also played confounding roles.

Furthermore, providers were forced to practice outside of guideline recommendations at times, because of patients living in rural parts of the state and difficulties with transportation.

Currently, our institution has transitioned to a different computer system that has streamlined several processes. An analysis of G-CSF utilization after the implementation of the pharmacist reference would add strength to this review and would provide a basis for future management of patients who receive G-CSFs.

**Conclusion**

The use of G-CSF therapy has been shown to improve outcomes in the prevention of febrile neutropenia in patients who receive chemotherapy and have a >20% risk for the disease. G-CSFs are the treatment of choice for reducing neutropenia and decreasing its severity; however, overutilization has been extensively reported with the use of G-CSF therapy. The current guidelines recommend the use of G-CSF support after chemotherapy in patients who receive chemotherapy and have a >20% risk for febrile neutropenia or who have a 10% to 20% risk as well as specific comorbidities. Systemwide protocols, electronic medical record alerts, and staff education may aid in the optimal use of these agents and may reduce healthcare expenditures.

G-CSF therapy may be warranted in patients who do not meet current guidelines criteria, and these patients should be assessed on a case-by-case basis. A collabora-
tion between the providers, board-certified oncology pharmacists, and staff would ensure proper management of patients who receive G-CSFs, by limiting inappropriate administration of these drugs and ensuring the administration of a G-CSF when indicated, to reduce the additional treatment-related costs.

Author Disclosure Statement

Dr Hanna is Consultant to Seattle Genetics and Hy­loris Pharmaceuticals, is on the Speakers’ Bureau of Seattle Genetics and AbbVie, and received Advisory Board funding in 2018-2019. Dr Mancini is on the Speakers’ Bureau of Takeda and is Consultant to Taiho Pharmaceuticals. Dr Wilson is on the Speakers’ Bureau of Merck. Dr Zuck­ern­man has no conflicts of interest to report.

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