ORIGINAL RESEARCH

Outcomes in Patients With Curative Malignancies Receiving Filgrastim as Primary Prophylaxis

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Background: Granulocyte colony-stimulating factor (G-CSF) prophylaxis has been shown to reduce the risk and duration of chemotherapy-induced neutropenia and febrile neutropenia (FN) and is recommended for at-risk patients receiving chemotherapy. Within the South Texas Veterans Health Care System (STVHCS), daily filgrastim injections remain the preferred formulation of G-CSF for primary prophylaxis of FN.

Methods: This retrospective, single-center cohort study from September 2015 to September 2020 included 59 patients who received daily filgrastim as primary prophylaxis with a curative cancer diagnosis and a chemotherapy regimen. Patients had either a high risk for FN or a chemotherapy regimen with an intermediate risk for FN and additional risk factors. The primary outcome was the incidence of neutropenia/FN leading to treatment delays. Secondary outcomes included chemotherapy dose decreases or discontinuations, hospitalizations, days of hospitalization, infections, extended duration of filgrastim, and transitions to pegfilgrastim due to neutropenia/FN.

Results: Patients received a median (IQR) of 7 (5-10) doses of filgrastim for primary prophylaxis. Overall, 10 (17%) patients experienced treatment delays due to neutropenia/FN. Fifteen (25%) patients were hospitalized with a median (IQR) length of stay of 5 (4-7) days, 9 (15%) patients had documented infections, and 2 (3%) patients required a chemotherapy dose reduction. Additionally, 9 (15%) patients required an additional median (IQR) of 2 (2-5) doses of filgrastim, and 9 (15%) patients were transitioned to pegfilgrastim.

Conclusions: These results suggest that additional measures such as tracking postnadir absolute neutrophil counts should be performed to ensure patients receive an appropriate number of filgrastim doses to prevent complications associated with neutropenia/FN.

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Febrile neutropenia (FN) frequently occurs in patients receiving chemotherapy, with the greatest risk of complications occurring in those who experience profound and prolonged neutropenia. Although granulocyte colony-stimulating factor (G-CSF) prophylaxis has been shown to reduce the risk and duration of chemotherapy-induced neutropenia and FN, there is no well-established optimal regimen.[1] The 2022 National Comprehensive Cancer Network (NCCN) guidelines for hematopoietic growth factors recommend prophylaxis with G-CSF in at-risk patients receiving chemotherapy, specifically in chemotherapy regimens considered high risk for FN (incidence > 20%) or intermediate risk for FN (incidence 10% to 20%) with additional patient risk factors.[2] The incidence of developing FN with at least 1 chemotherapy cycle is estimated at 10% to 50% of patients with solid tumors and > 80% of patients with hematologic malignancies.[3] The rate of major complications (eg, hypotension, acute renal, respiratory, or heart failure) in the context of FN is 25% to 30%, and mortality is reported up to 11% in this population.[4]

Because of the significant consequences of neutropenia and FN, prevention is imperative due to the increase in morbidity and mortality, including chemotherapy delays, increased hospitalizations, chemotherapy dose reductions, and discontinuations that cause delays in care.[5] In patients with curative malignancies, these consequences can negatively impact treatment efficacy and overall survival. Additionally, infections occur in 20% to 30% of patients with febrile episodes. Although fever is often the only clinical sign or symptom of infection, patients who are profoundly neutropenic may present with suspected infection and be afebrile or hypothermic.[3]

For filgrastim, the NCCN guidelines do not specify the total days of required injections, but state that a daily dose should be given until the postnadir absolute neutrophil count (ANC) recovers to normal or near normal levels by laboratory standards.[2] It is uncommon in clinical practice to track postnadir ANCs due to frequent laboratory monitoring. Clinical trial data suggest an average duration of 11 days of daily filgrastim injections for ANC recovery; however, real-world data exist supporting a range from 4 to 10 days with a median of 7 injections per

TABLE 1 Patient Baseline Characteristics (N = 59)

Characteristics	Results
Age, median (IQR), y	64 (55-70)
Sex, No. (%)	
Male	42 (71)
Female	17 (29)
Race, No. (%)	
African American	11 (19)
White	37 (62)
Malignancy type, No. (%)	
Non-Hodgkin lymphoma	30 (51)
Breast	19 (32)
Gastric	2 (3)
Hodgkin lymphoma	2 (3)
Other	6 (11)
Chemotherapy regimen, No. (%)	
R-CHOP	21 (36)
ddAC	11 (19)
TC	7 (12)
R-ICE	6 (10)
DA R-EPOCH	2 (3)
R-Hyper CVAD	2 (3)
Other	10 (17)
FN risk, No. (%)	
High	33 (56)
Intermediate	26 (44)
Factors in intermediate FN risk, No. (%)	
Prior chemotherapy or radiation	9 (35)
Persistent neutropenia	0 (0)
Bone marrow involvement by tumor	22 (85)
Recent surgery and/or open wounds	0 (0)
Liver dysfunction (bilirubin > 2 mg/dL)	1 (4)
Renal dysfunction (creatinine clearance < 50 mL/min)	4 (15)
Age > 65 y and full chemotherapy dose	16 (62)
Filgrastim therapy duration, No. (%)	
5 d	11 (19)
7 d	46 (78)
10 d	2 (3)

Abbreviations: DA R-EPOCH, rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; ddAC, dose-dense doxorubicin, cyclophosphamide; FN, febrile neutropenia; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-Hyper CVAD, rituximab, cyclophosphamide, vincristine, doxorubicin, dexamethasone; R-ICE, rituximab, ifosfamide, carboplatin, etoposide; TC, docetaxel, cyclophosphamide.

cycle for prevention of neutropenia or FN.[6,7]

At the South Texas Veterans Health Care System (STVHCS) in San Antonio, daily filgrastim injections are preferred due to cost; patients typically receive a 7-day course for primary prophylaxis for FN. In our study, we aimed to determine the outcomes in patients receiving daily filgrastim injections with a curative cancer diagnosis and a chemotherapy regimen with either high risk for FN, or a chemotherapy regimen with an intermediate risk for FN and additional patient risk factors. Before the initiation of data collection, this study was reviewed and determined to be exempt by the University of Texas Health Science Center at San Antonio Institutional Review Board.

METHODS

STVHCS electronic health record reviews were performed to identify patients who received filgrastim primary prophylaxis (defined as filgrastim, tbo-filgrastim, or filgrastim-sndz) for a curative cancer diagnosis. Primary prophylaxis refers to the administration of G-CSF in the first cycle of chemotherapy before the onset of neutropenia. Patients received filgrastim prophylaxis if they were undergoing treatment with a chemotherapy regimen with either high risk for FN or a chemotherapy regimen with an intermediate risk for FN and additional patient risk factors. Risk factors for patients included prior chemotherapy or radiation therapy; persistent neutropenia; bone marrow involvement by tumor; recent surgery and/or open wounds; liver dysfunction (defined as total bilirubin > 2 mg/dL); renal dysfunction (defined as creatinine clearance < 50 mL/min); and those aged > 65 years receiving full chemotherapy dose intensity. Neutropenia is defined as a decrease in ANC < 1000 neutrophils/μL, whereas FN is defined as a single temperature of > 38.3 °C or > 38.0 °C for longer than 1 hour with < 500 neutrophils/μL or < 1000 neutrophils/μL predicted to decline to < 500 neutrophils/μL over the next 48 hours. All patients had their filgrastim dispensed for home administration during their chemotherapy appointment.

Patients were included if they received filgrastim for primary prophylaxis of FN with a curative cancer diagnosis. Patients receiving salvage chemotherapy for hematologic malignancies with intent to proceed to curative transplant were also included. Bone marrow involvement of the tumor is a FN risk factor. Only patients with hematologic malignancies and bone marrow involvement were included. Patients were excluded if they received filgrastim for secondary prophylaxis of neutropenia or FN, a noncurative cancer diagnosis, stem cell transplant mobilization and engraftment, or nononcologic neutropenia.

The primary outcome for this study was

TABLE 2 Study Outcomes (N = 59)

Outcomes	Results
Primary	
Chemotherapy dose delays, No. (%)	10 (17)
Secondary	
Chemotherapy dose decreases, No. (%)	2 (3)
Chemotherapy dose discontinuations, No. (%)	0 (0)
Hospitalizations, No. (%)	15 (25)
Length of hospitalization, median (IQR), d	5 (4-7)
Infections, No. (%)	9 (15)
Extended duration of filgrastim, No. (%)	9 (15)
Transition to pegfilgrastim, No. (%)	9 (15)

the incidence of neutropenia or FN leading to treatment delays despite the use of primary prophylaxis with filgrastim. A dose delay was defined as a delay of planned chemotherapy by ≥ 3 days. Secondary outcomes included chemotherapy dose decreases or discontinuations, hospitalizations, days of hospitalization, infections, extended duration of filgrastim, and transitions to pegfilgrastim due to neutropenia or FN. Documented infections were defined in patients with a positive culture, laboratory testing, or imaging consistent with infection. Extended durations of filgrastim or transitions to pegfilgrastim were patient specific and upon clinician discretion.

Descriptive statistics were used to summarize the study population and their health outcomes. Fisher exact test was used to compare FN incidence for high- and intermediate-risk FN groups.

RESULTS

Between September 1, 2015, and September 24, 2020, 381 patients received filgrastim. Of these patients, 59 met the inclusion criteria. Patients receiving filgrastim were excluded due to stem cell transplant mobilization/engraftment (n = 145), a noncurative cancer diagnosis (n = 134), use as a secondary prophylaxis (n = 33), and nononcologic neutropenia (n = 8). Additionally, 2 patients initially received pegfilgrastim and were not included in this data set.

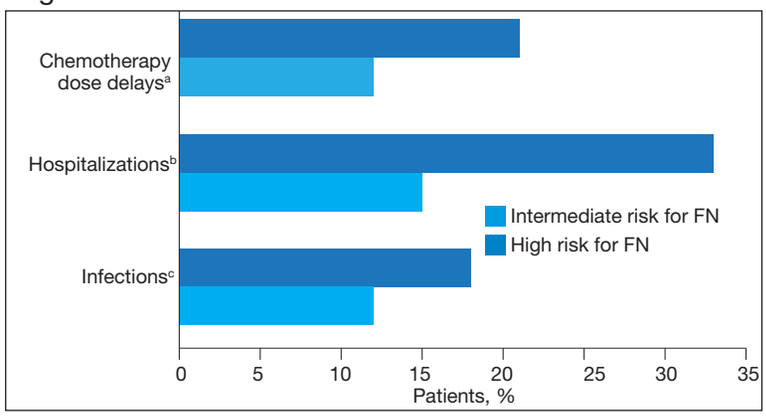
The median age for patients was 64 years and 42 (71%) were male (Table 1). Thirty (51%) patients had non-Hodgkin lymphoma and 19 (32%) had breast cancer. There were 33 (56%) patients with high-risk chemotherapy regimens and 26 (44%) with an intermediate-risk regimen. Overall, 48 (81%) patients received 7 or 10 days. and 11 (19%) patients received 5 days of filgrastim therapy.

Ten (17%) patients experienced dose delays despite filgrastim use (Table 2). This included 7 (21%) patients in the high risk for FN group and 3 (12%) patients in the intermediate risk for FN group (P = .49). Additionally, 15 (25%) patients were hospitalized with either neutropenia or FN despite filgrastim use. This included 11 (33%) patients in the high risk for FN group and 4 (15%) patients in the intermediate risk for FN group (P = .14). The median (IQR) duration of hospitalization was 5 (4-7) days. Two patients with acute lymphocytic leukemia and acute myeloid leukemia (AML) on regimens deemed high risk for FN had multiple hospitalizations despite filgrastim use and were hospitalized for a total of 16 and 17 days, respectively. Both transitioned to pegfilgrastim after their subsequent hospitalizations with successful continuation of treatment.

Nine patients (15%) had the number of filgrastim injections per chemotherapy cycle extended due to various reasons. Five patients required extended days after hospitalization for FN, 3 patients for dose delays due to neutropenia with the previous cycle, and 1 patient with an undocumented reason outside of the prespecified outcomes. Two of these patients experienced continued neutropenia and dose delays after extending filgrastim from 5 to 7 days or 7 to 10 days. One patient who experienced continued neutropenia after extending filgrastim to 10 days was subsequently transitioned to pegfilgrastim without further episodes of neutropenia. The other patient who still experienced neutropenia after extending filgrastim to 7 days was receiving the last chemotherapy cycle and did not require subsequent doses of filgrastim.

Two additional patients were not included in the hospitalizations. The first was a patient on a chemotherapy regimen with a high risk for FN who presented to the emergency department with documented FN but was never admitted since the patient elected to not be hospitalized. This patient developed oral, anal, and vaginal candidiasis, and it was noted by the oncologist at the next clinic visit that this was likely secondary to grade 4 neutropenia (ANC < 500 neutrophils/μL). The second was a patient on a chemotherapy

FIGURE Patient Outcomes Stratified by Chemotherapy Regimen Risk for FN



Abbreviation: FN, febrile neutropenia.
[a]*P* = .49
[b]*P* = .14
[c]*P* = .72

regimen with an intermediate risk for FN who was already hospitalized but had developed FN and sepsis despite filgrastim use.

Finally, out of the hospitalized patients, 9 (15%) had infections. This included 6 (18%) patients in the high risk for FN group and 3 (12%) patients in the intermediate risk for FN group (*P* = .72) (Figure). Six patients transitioned to pegfilgrastim for hospitalization, 2 for neutropenia, and 1 for an unspecified reason. Overall, 9 (15%) patients who received filgrastim ended up transitioning to pegfilgrastim; 6 (67%) of these patients were transitioned due to hospitalization for FN. Of all the patients who transitioned to pegfilgrastim, 1 patient on a high risk for FN regimen developed sepsis due to herpes zoster in the setting of neutropenia after the previous cycle of chemotherapy.

DISCUSSION

Real-world data are limited regarding G-CSF practice patterns; however, available data demonstrate patients may receive suboptimal treatment courses of filgrastim leading to increased complications associated with neutropenia and FN, such as dose delays and hospitalizations.[8,9] At STVHCS, 48 (81%) patients received a filgrastim course of ≥ 7 days as an initial course for primary prophylaxis. Multivariate analyses performed by Weycker and colleagues described a decreased risk of hospitalization for neutropenia or FN with each additional day of filgrastim prophylaxis; however, such analysis could not be performed in our data set due to the small sample size.[8] In this retrospective review, 10 (17%) patients experienced treatment delays due to neutropenia or FN, mirroring previously published data. The hospitalization rate of 25% is higher than the published incidence of 5.2% of cancer-related hospitalizations among adults.[7,10] This difference may be explained by a difference in health care access for the veteran population.

As an alternative to daily filgrastim injections, NCCN also recommends a single dose of pegfilgrastim for primary prevention of FN. Efficacy benefits of pegfilgrastim use include increased patient adherence due to a single injection, a reduction in FN incidence and FN-related hospitalizations, and improved time to ANC recovery compared with filgrastim.[11] There are reports suggesting pegfilgrastim significantly reduces neutropenia and FN incidence to a greater extent compared with daily filgrastim injections.[6] In patients with breast cancer receiving dose-dense adjuvant chemotherapy, there are data demonstrating that patients who received filgrastim were more likely to experience severe neutropenia, dose reductions, and treatment delays leading to lower dose density compared with pegfilgrastim.[12] Of the 19 patients with breast cancer included in our population, 26% experienced one of the previously described outcomes leading to either extensions of daily filgrastim injections or transitions to pegfilgrastim to successfully maintain dose density. In patients with AML receiving consolidation chemotherapy, filgrastim was found to be associated with a statistically significant increased risk of hospitalizations compared with pegfilgrastim.[13] The one patient with AML included in our study did not require additional hospitalizations for neutropenia or FN after transitioning to pegfilgrastim.

Given the cost advantage, STVHCS continues to prefer daily filgrastim injections. A recent survey demonstrated that 73% of patients at 23 sites in the Veterans Health Administration used filgrastim rather than pegfilgrastim for cost savings, although it is recognized that daily filgrastim injections are less convenient for patients.[14] This analysis did not review costs associated with hospitalization for FN or the appropriateness of G-CSF use. Cancer-related neutropenia accounts for 8.3% of all cancer-related hospitalization costs among adults; the average

hospitalization costs nearly $25,000 per stay and about $2.3 billion among for adult patients with cancer annually.[10,15]

Limitations

This study has limitations that affected the applicability and interpretation of the results. This included the study design since it was a retrospective, single-center, descriptive cohort study. Patient adherence to daily filgrastim injections could not be assessed due to the retrospective nature of the study. The small sample size of 59 patients was prohibitive for utilization of additional analytical tools. Additionally, the predominately male veteran population may make applicability to non-VA populations restrictive.

CONCLUSIONS

Based on the incidence of primary and secondary outcomes associated with using daily filgrastim injections as primary prophylaxis in this study, additional measures such as tracking postnadir ANCs should be performed to ensure patients receive an appropriate number of filgrastim doses to prevent complications associated with neutropenia.

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Ethics and consent

This study was deemed by the local institutional review board (The University of Texas Health Science Center at San Antonio) to be exempt from review before the initiation of data collection; it was deemed nonregulated research as this was a quality improvement project.

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