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Appropriateness of using granulocyte colony-stimulating factor (G-CSF) for primary prophylaxis of febrile neutropenia in solid tumors

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Abstract

Introduction: Febrile neutropenia (FN) is one of the dose-limiting adverse effects of chemotherapy. Granulocyte-Colony Stimulating Factors (G-CSFs) minimize the incidence of FN and reduce the risk of neutropenia complications. This study was conducted to address the prescription pattern of G-CSF for primary prophylaxis of FN during the first cycle of chemotherapy in solid tumors.

Method: This prospective observational study was done to investigate the G-CSF prescription pattern in patients receiving the first cycle of chemotherapy for solid tumors and compare it with the NCCN guideline recommendations.

Result: Based on the guideline, prophylactic G-CSF administration was indicated in 26 of the 96 patients (27.1%) and all of them received G-CSF. On the other hand, 70 patients (72.9%) did not meet the guideline criteria for prophylaxis, but 60 (62.5%) of them received G-CSF. Seven doses of pegfilgrastim and 165 doses of filgrastim were used inappropriately in the study population, which was associated with an economic burden of about 224.7 million IRR (5350 USD).

Conclusion: Taken together, inconsistencies with the guideline were observed in this prospective evaluation, suggesting that submitting rationalized policies to decrease G-CSF prescription, especially in patients with a lower or intermediate FN risk, yields substantial cost savings.

Keywords

Cost, febrile neutropenia, granulocyte-colony stimulating factors, rational prescription, solid tumor

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Introduction

Neutropenia is defined as an absolute neutrophil count below 0.5×10^9/L which can progress to febrile neutropenia (FN). FN is one of the dose-limiting adverse effects of chemotherapy that may result in dose reductions or treatment delays. It also inevitably increases the costs associated with diagnosis and treatment procedure, and contributes to early morbidity and mortality.[1–3]

Granulocyte-Colony Stimulating Factors (G-CSFs) regulate the differentiation and activation of neutrophils. When used during dose-intensive chemotherapy, G-CSFs minimize the incidence of FN and reduce the

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risk of neutropenia complications resulting in a better response and improved overall survival.[4] On the other hand, G-CSFs are not indicated in all chemotherapy regimens and their administration imposes a significant financial burden on the health-care system.[4]

International organizations, such as the National Comprehensive Cancer Network (NCCN), define the risk of neutropenia based on the chemotherapy regimen and individual risk factors.[5,6] G-CSF is indicated in solid tumors chemotherapy as a primary FN prophylaxis when the overall risk of FN is approximately 20% or greater. For those with an intermediate FN risk (10–20%), additional factors need to be considered prior to administration of G-CSF. Furthermore, there are several circumstances in which the benefits of G-CSF therapy must be weighed against its significant financial burden on the health-care system and side effects. Although some life-threatening side effects such as splenic rupture and allergic reactions have been reported with G-CSF use, the main toxicity is limited to mild to moderate bone pain.[7] Current guidelines discourage the use of G-CSF following chemotherapy with palliative intent or in regimens with an overall FN risk of $<10\%$.[4–6,8,9]

Concerns about the high cost of G-CSFs along with the limited adherence of physicians to clinical practice guidelines have resulted in studies to examining the status of adherence to guidelines in current clinical practice.[10–12] In Iran, the price of pegfilgrastim and filgrastim is 5,700,000 IRR (135.7 USD) and 1,120,000 IRR (26.7 USD) per dose, respectively.[a] While the addition of G-CSF to treatment regimen may decrease the hospitalization costs and financial impacts of FN, it inevitably raises the drug costs. In a cohort study, overutilized G-CSF cost about $712,264 in a year.[11]

G-CSF utilization has not yet been critically evaluated in our institute; therefore, this study was conducted to address the prescription pattern of G-CSF for primary prophylaxis of FN during the first cycle of chemotherapy in solid tumors.

Method

This prospective observational study was performed at the Cancer Institute of Imam Khomeini Hospital Complex affiliated with Tehran University of Medical Science between July and September 2018. The patients who aged 18 years and above who were referred to the Institute to receive the first cycle of chemotherapy for a type of solid tumor were included.

Data collection was performed prospectively by a pharmacist under the supervision of a clinical pharmacist. The study sample size was calculated at 96 patients assuming a drug utilization review in 2008 that reported a 53% compliance with the guideline.[13] Patients' information including demographic and laboratory data, diagnosis, chemotherapy regimen, prescribed G-CSF doses and number, and FN risk factors were recorded for analysis and compared with NCCN guideline recommendations.

FN risks associated with specific chemotherapy regimens were derived from the NCCN guideline and previous studies.[6,14]G-CSF prescription was considered appropriate as primary prophylaxis if the patient received a chemotherapy regimen associated with a high-risk of developing FN (overall risk $\geq$20%) or an intermediate FN risk (overall risk 10–20%) with at least one risk factor. Risk factors included renal dysfunction (creatinine clearance $<$ 50 ml/min), liver dysfunction (bilirubin $>$2.0 mg/dL), age $>$65 years, previous chemotherapy or radiotherapy, persistent neutropenia, bone marrow involvement with tumor, previous infection or open wound, recent surgery, poor performance status (Karnofsky performance score $<$70), and HIV infection.[6,14] The incidence of FN and neutropenia was calculated on the first day of the second cycle.

Descriptive statistics are used to summarize the results for primary outcomes. Data analysis was performed using the SPSS Software version 25.0 and the Stata Software version14.

Results

A total of 96 patients, 52 females and 44 males, met the inclusion criteria and were enrolled in the study. The main underlying cancers were colorectal cancer and breast cancer in 20 (20.8%) and 19 (19.8%) of patients, respectively. The most commonly prescribed regimens were AC (Doxorubicin-Cyclophosphamide) in breast cancer and FOLFOX (Oxaliplatin-Leucovorin-Fluorouracil) in colorectal cancer patients (15 patients). Detailed information on the study population is shown in Table 1.

Eighty-six out of 96 patients received G-CSF after chemotherapy. Two different formulations of G-CSF were prescribed; a prefilled syringe containing 300 mcg filgrastim, which was administered to 73 patients, and a prefilled syringe containing 6 mg of the pegylated form, which was prescribed for 13 patients.

Based on the guideline, 26 out of the 96 patients (27.1%) had the indication for prophylactic G-CSF use; 21 patients had chemotherapy regimens with a high FN risk and 5 had an intermediate FN risk with additional risk factors. All of these patients received G-CSF. On the other hand, 70 patients (72.9%) did not meet the above criteria for primary prophylaxis, of whom 60 (62.5%) received G-CSF (Table 2).

Cohen's κ was run to determine if there was an agreement between guideline recommendations and

Table 1. Information of the study population.

Gender	52 (54.1)
Female; *N* (%)	44 (45.9)
Male; *N* (%)	
Age (years)	
Range	18–84
Mean ± SD	53.6 ± 13.4
Type of cancer and common regimens *N* (%)	
Colorectal cancer	20 (20.8)
Oxaliplatin-Leucovorin-Fluorouracil	15 (75.0)
Other regimens	5 (25.0)
Breast Cancer	19 (19.8)
Doxorubicin-Cyclophosphamide	9 (47.4)
Dose-dense Doxorubicin-Cyclophosphamide	6 (31.6)
Other regimens	4 (21.0)
Oesophagogastric Cancer	17 (17.7)
Docetaxel-Fluorouracil-Cisplatin	5 (29.4)
Epirubicin-Oxaliplatin-Capecitabine	3 (17.6)
Docetaxel-Oxaliplatin-Fluorouracil	3 (17.6)
Oxaliplatin-Leucovorin-Fluorouracil	2 (11.8)
Other regimens	4 (23.6)
Soft Tissue and Bone Sarcoma	12 (12.5)
Doxorubicin-Ifosfamide-Mesna	6 (50.0)
Ifosfamide-Etoposide-Mesna	2 (16.7)
Doxorubicin-Dacarbazine	2 (16.7)
Other regimens	2 (16.7)
Lung Cancer	7 (7.2)
Taxan-Carboplatin	2 (33.3)
Taxan-Gemcitabine	2 (33.3)
Pemetrexed-Carboplatin	2 (33.3)
Etoposide-Cisplatin	1 (14.3)
Ovarian Cancer	6 (6.3)
Paclitaxel-Carboplatin	6 (100)
Pancreatic Cancer	6 (6.3)
Irinotecan-Oxaliplatin-Leucovorin-Fluorouracil	2 (33.3)
Other regimen	4 (66.7)
Hepatobiliary Cancer	4 (4.1)
Gemcitabine-Cisplatin	3 (75.0)
Gemcitabine-Oxaliplatin	1 (25.0)
Other cancers	5 (5.2)

G-CSF prescription showed a poor agreement ($\kappa = 0.07$, $p = 0.09$).

The timing of G-CSF administration was 24 to 48 hours after cessation of chemotherapy in all patients, which was compatible with the guideline recommendation. The duration of G-CSF administration in patients who had G-CSF indication varied from two to seven doses (Table 3).

Seven doses of pegfilgrastim and 165 doses of filgrastim were used in patients who did not have any indications for primary prophylaxis which was associated with an economic burden of about 224.7 million IRR (5350 USD).

The next chemotherapy cycle was delayed in three patients due to neutropenia, and all of them received a regimen with high FN risk and received three doses of G-CSF.

Discussion

G-CSF administration reduces the incidence of FN, need for hospitalizations and broad-spectrum antibiotics, and improves the rate of full-dose cytotoxic chemotherapy given on schedule.[15]

Recent studies have reported widespread G-CSF prescription for FN prophylaxis which is not consistent with guidelines.[15–20] Inconsistencies with the guidelines include both overuse and underuse of G-CSF. In the study by Alshehri et al. in Saudi Arabia,[19] although about 85% of patients who received prophylactic G-CSF had indication for prophylaxis, 28 out of 29 high-risk patients did not receive G-CSF. Likewise, in a study conducted by Zullo et al. in the United States, nine out of 15 patients who were treated with a chemotherapy regimen with high FN risk did not receive G-CSF.[21] This is while all patients with high FN risk in our study received prophylactic G-CSF. Of note, G-CSF was administered to 60 (62%) patients with no indication and over utilization was a more important inconsistency with the guideline recommendations in our study. Butler reported that 60% of the patients who received G-CSF had a chemotherapy regimen with less than 20% risk for neutropenia. In addition, 50% of the patients with less than 10% FN risk received G-CSF.[22] Similarly, in our study, 44 out of 53 patients (83%) with less than 10% risk for FN and 95% of the patients with an intermediate FN risk without risk factors received G-CSF. Since the evidence supporting G-CSF use in patients with an intermediate FN risk is mixed, and the recommendations are mainly based on expert opinion, noncompliance with available guidelines in such cases does not necessarily indicate misuse.[6]

Administration of G-CSF should begin 24 to 72 hours after the last dose of chemotherapy.[6] Although the timing of G-CSF was correct in all patients in whom primary prophylaxis was indicated, the duration of G-CSF administration varied significantly and ranged from two to seven days after the chemotherapy. Although all patients in whom primary prophylaxis was indicated received G-CSF, almost all patients received G-CSF for less than seven days from the duration appropriateness standpoint. The guideline

Table 2. Neutropenic fever prophylaxis in the study patients.

	FN risk category			
	High (>20%)	Intermediate (10–20%) with risk factor	Intermediate (10–20%) without risk factor	Low (<10%)
Number of patients	21	5	17	53
Number of patients who received G-CSF	21	5	16[a]	44[a]
Appropriateness based on guideline (%)	100	100	0.05	16.98

[a]No indication based on the NCCN guideline for myeloid growth factors prescription

Table 3. G-CSF doses prescribed in patients who had indication for primary prophylaxis.

Number of prescribed G-CSF for each patient ($N = 26$)	N (%)
1 dose of pegfilgrastim	7 (26.92)
1 dose of filgrastim	0 (0.0)
2 doses of filgrastim	2 (7.69)
3 doses of filgrastim	10 (38.46)
4 doses of filgrastim	5 (19.23)
5 doses of filgrastim	0 (0.0)
6 doses of filgrastim	1 (3.84)
7 doses of filgrastim	1 (3.84)

suggested continuing G-CSF through post-nadir ANC (absolute neutrophil count) recovery, which means typically about 10–11 days after the chemotherapy cycle.[23] Premature discontinuation of G-CSF is less effective in FN prevention. In a study conducted in 2016, half of the patients who were hospitalized due to FN had received prophylactic G-CSF for less than 7 days.[24] Likewise, reduced risk of hospitalization for neutropenia or infection was seen with each additional day of prophylaxis with G-CSF in different cancers.[25] Although FN did not occur in any patient during the study, chemotherapy was delayed in three patients due to neutropenia without fever, and all of them were at high risk for FN and had already taken three doses of G-CSF. Based on the guideline recommendation, it is reasonable to monitor blood counts twice weekly, until an adequate neutrophil count is achieved. However, this is not a routine practice in our wards unfortunately.[6,14,26] Due to ANC monitoring difficulties and poor patients' compliance in our practice settings, pegfilgrastim is a reasonable choice for chemotherapy regimens given every two or three weeks.[17] Indeed, in a study in Italy, pegfilgrastim was more cost-effective compared to six-day filgrastim in breast cancer patients.[26]

Overutilization of G-CSF in patients with a low and intermediate FN risk in this study was associated with an economic burden of about 224.7 million IRR (5350 USD). In a cohort study of 256 patients conducted in 2013, the authors claimed that more than 600,000 USD could be saved if G-CSF was only administered in patients with high FN risk.[27]

Taken together, in this prospective evaluation, inconsistency with the guideline recommendations in both indication and dosing were noticed, suggesting that submitting rationalized policies such as educational program and protocol implementation to decrease G-CSF prescription yields substantial cost savings, especially in patients with a low or intermediate FN risk.

Finally, a number of important limitations should be considered. First, our study was relatively small and was conducted in a single academic center; therefore, the results may not be generalized to other centers. Second, the impact of chemotherapy intent, whether curative or palliative, on the pattern of G-CSF use was not evaluated. It would be interesting to assess the effect of between-physician heterogeneity and chemotherapy intent on the appropriateness of G-CSF use.

Conclusion

This prospective study was conducted to evaluate the appropriateness of G-CSF use for the primary prophylaxis of FN in the real-world practice. It was found that G-CSF was overused for the primary prophylaxis of FN in chemotherapy for solid tumors which necessitates appropriate pharmacists' interventions such as protocol implementation as well as educational programs for rationalization of its use.

Authors' contribution

It is stated that all the authors listed in this letter and the article have scientifically contributed significantly to do this research. Also they are all aware and consented to submit this article to Journal of oncology *Pharmacy Practice*. The manuscript was reviewed and approved by all the authors.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: All authors listed in this page have scientifically contributed to do this research. Also their consent was obtained to submit this article to Journal of oncology Pharmacy Practice. The manuscript is reviewed and approved by all the authors and no conflicts of interests have been declared.

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a. http://irc.fda.gov.ir/nfi. 2018

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