ORIGINAL ARTICLE

Prescribing Pattern of Granulocyte Colony-stimulating Factor at Tertiary Care Hospital in Riyadh: An Observational Study

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Abstract

Background and Aim: Febrile neutropenia (FN) is one of the lethal side effects that necessity hospitalization with fever and life-threatening infections in patients receiving chemotherapy. Several regulatory guidelines recommend the prophylactic use of granulocyte colony-stimulating factor (G-CSF) to overcome this situation. However, rational use of G-CSF is required to avoid economic burden and undesired side effects such as thrombocytopenia. Hence, the current study was designed to evaluate the pattern of G-CSF utilization in our hospital and subsequently assess the appropriateness of its prescription with an estimation on cost factor. **Materials and Methods:** This is a prospective observational study conducted between December 2017 and February 2018 in the chemotherapy day unit of Prince Sultan Military Medical City, Riyadh, Saudi Arabia, on patients diagnosed with any type of cancer and receiving chemotherapy with G-CSF. The appropriate use of G-CSFs for FN prophylaxis was evaluated based on the American Society for Clinical Oncology (ASCO) guidelines and published data. The demographic, clinical data and G-CSF prescribing data were collected by the clinical pharmacist from patient's files and the electronic records. The data were analyzed by appropriate statistical tests using SPSS-IBM 23. **Results:** Of 118 patients who fulfill our inclusion criteria, 26% and 15% of them were breast cancer and colorectal cancer patients, respectively. Based on the ASCO guidelines and published literature, only 42.4% of them were considered appropriate for G-CSF prescription, while 57.6% of them received G-CSF inappropriately. The major reasons for inappropriate prescription were unfamiliarity with chemotherapy regimens or physicians' anticipated risk of neutropenia in patients receiving chemotherapy. Due to inappropriate prescription, around 61.70% of the cost of G-CSF was wasted. **Conclusion:** Inadequate knowledge of the chemotherapy risk of FN was documented as major reason for inappropriate prescription of G-CSF. Health-care professionals including clinical pharmacists should play an active to improve G-CSF prescribing pattern. In addition, availability of comprehensive hospital guidelines may rationalize the therapeutic approach in G-CSF prescription.

Key words: Cancer, chemotherapy, febrile neutropenia, granulocyte colony-stimulating factor, Riyadh

INTRODUCTION

One of the most common dose-limiting toxicities in several chemotherapy regimens is febrile neutropenia (FN).[1] This fatal condition is associated with increase hospitalization due to fever and infection after chemotherapy.[2] In addition, FN episodes in cancer patients may force the health-care professionals to reduce the chemotherapy dose that itself may cause death from cancer.[3] A retrospective study on breast cancer patients shows a higher survival rate (40%) in patients who received normal planned therapeutic dose when compare to those who were given lower than normal dose (21%).[4]

Granulocyte colony-stimulating factors (G-CSFs) are one of the medications that are used to prevent incidents of FN in patients receiving chemotherapy. It works by augmenting production as well as activation of neutrophils and facilitates their migration.[5] Krzemieniecki *et al*., 2014,[6] reported higher incidence of FN in patients who were not given G-CSF compared to those who received G-CSF along with

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chemotherapy regimen. The three currently used G-CSFs are filgrastim, pegfilgrastim, and lenograstim. As per the oncology practice based on literature and guidelines, while filgrastim and lenograstim are given by daily injection with an average of 11 injections in one chemotherapy cycle;[7] pegfilgrastim is suggested as a single injection in each chemotherapy cycle.[8] In oncology practice, G-CSFs are either administered as primary prophylaxis (all chemotherapy cycles starting from cycle 1) or as secondary prophylaxis (in remaining cycles after an FN).

The American Society of Clinical Oncology (ASCO),[9] the National Comprehensive Cancer Network,[10] and the European Organization for Research and Treatment of Cancer[11] recommend use of primary prophylaxis with G-CSFs in patients undergoing chemotherapy regimen with ≥20% risk of developing FN. For chemotherapy regimens associated with intermediate risk of FN (10–20%), the ASCO guidelines recommend not to use G-CSFs unless patients display poor renal function, liver dysfunction, advanced age (>65 years), previous chemotherapy with neutropenia, previous radiation therapy with neutropenia, preexisting neutropenia or bone marrow involvement with tumor, previous infection or open wounds, recent surgery, poor performance status, or HIV infection. For low-risk FN chemotherapy regimens (<10%), it is not recommended to use G-CSFs. As stated above, the use of G-CSF is essential in number of chemotherapy regimens; however, its excessive use will not only lead to patients' exposure to toxic effects of G-CSF but also unnecessarily tend to add financial burden on patients and their caregivers. The previous research done elsewhere showed a high prevalence of inappropriate prescription of G-CSF,[12] whereas there is no such report available in public domain from our location. Therefore, this study was aimed to evaluate the pattern of G-CSF utilization in our hospital including filgrastim and pegfilgrastim and to assess the contributing factors as well as possible financial burden due to inappropriate prescribing of G-CSF.

MATERIALS AND METHODS

This is a prospective observational study conducted at Prince Sultan Military Medical City in Chemotherapy Day Unit, Central Region, Saudi Arabia. On obtaining institutional review board approval from the hospital (number 978, August 14, 2017), adult cancer patients, who visited chemotherapy day unit between December 1, 2017, and February 28, 2018, eligible for chemotherapy treatment and also prescribed with filgrastim or pegfilgrastim, were included in the study by purposive sampling.

A data collection standard form was developed, pretested, and modified. The components of this form were patient demographic details (medical record number, gender, age, weight, etc.), admitting diagnosis, dates of admission and discharge, prescribing data for the use of G-CSF (including indication, dose, dosing interval, route of administration, and duration of therapy), types of cancer and chemotherapy regimen, and laboratory data (including white blood cell [WBC] counts with differential counts, hemoglobin, platelet counts, and red blood cell). Absolute neutrophil count (ANC) was calculated for each patient (ANC= WBC × total neutrophils [segmented neutrophil % + segmented bands %] ×10). The appropriate use of G-CSFs for FN primary prophylaxis or secondary prophylaxis was evaluated based on the ASCO guidelines and published data.

G-CSFs prescription was considered appropriate in patient who received chemotherapy regimens associated with high risk (≥20%) of developing of FN or intermediate risk (10–20%) of FN with comorbidities or as secondary prophylaxis in patients developed FN from the previous cycle of chemotherapy.

The details of chemotherapy regimen based on published articles and guidelines are listed in Table 1. The appropriate and inappropriate criteria to evaluate the prescribing pattern of G-CSFs based on the ASCO guidelines and published articles applied in this research are given in Table 2.

The demographic, clinical data and G-CSF prescribing data were collected by the clinical pharmacist from patient's files and the electronic records. The data were analyzed by appropriate statistical tests using SPSS-IBM 23. $P < 0.05$ using Chi-square test was considered statistically significant.

Table 1: Chemotherapy regimen with risks for FN[13]

Chemotherapy regimen	FN risk
Docetaxel+Cyclophosphamide	>20%
5-fluorouracil+Epirubicin+Cyclophosphamide	>20%
Paclitaxel+Carboplatin+Trastuzumab q3w	10–20%
Docetaxel+Carboplatin+Trastuzumab	10–20%
Trastuzumab+Docetaxel	10–20%
Rituximab+Doxorubicin+Vinorelbine+Cyclophosphamide+prednisolone every 21 days	10–20%
Carboplatin+Gemcitabine	10–20%
Docetaxel+Carboplatin+Capecitabine	10–20%
Docetaxel+Cisplatin+Fluorouracil	10–20%

FN: Febrile neutropenia

Table 2: Appropriate and inappropriate criteria to evaluate the prescribing pattern of G-CSFs

Appropriate prescribing	1. Chemotherapy associated with high-risk FN 2. Chemotherapy associated with intermediate-risk FN with the following criteria (poor renal function, liver dysfunction, advanced age [>65 years], previous chemotherapy with neutropenia, previous radiation therapy with neutropenia, preexisting neutropenia, or bone marrow involvement with tumor, previous infection or open wounds, recent surgery, poor performance status, or HIV infection) 3. FN from previous cycle of chemotherapy (secondary prophylaxis)
Inappropriate prescribing	1. Chemotherapy associated with intermediate-risk FN (without the previous criteria) 2. Chemotherapy associated with low-risk FN

G-CSFs: Granulocyte colony-stimulating factors, FN: Febrile neutropenia

RESULTS

Demographic data of the participants

A total of 118 patients who met the inclusion criteria were included in the study. In this study, 61.8% of the participants were female, whereas 38% of them were male with an overall median age of 49 years. The distribution of patients based on the cancer type is given in Figure 1. Most of the participants of this study were breast cancer and colorectal cancer patients, 26% and 25.4%, respectively followed by this were the patients with non-Hodgkin lymphoma (15.25%) and Hodgkin's lymphoma (14.40%).

As shown in Figure 2, 42.3% of the patients who participated in our study had a low risk for developing FN (<10%), while only 0.84% of them possess high risk (≥20%) for FN. Majority of the patients (56.70%) in this study were in an intermediate risk (10–20%) for FN development.

Appropriateness of G-CSF prescription

While evaluating the patient on appropriateness of G-CSF prescription based on criteria listed in Table 2, we found only 50 patients fulfill the criteria which account for nine patients in primary prophylaxis and 41 in secondary prophylaxis (7.6% and 34.7% in primary and secondary prophylaxis, respectively). As shown in Figure 3, 68 patients were given G-CSF inappropriately which represents 57.6% of the participants. The differences, appropriate and inappropriate prescribing pattern of G-CSF along with chemotherapy in cancer patients, were found to be statistically significant ($P < 0.0001$). The mean duration of G-CSF was 4.32 (standard deviation ± 1.89) days.

Physicians' feedback on G-CSF prescription

When prescribing physicians were requested to explain the possible reasons for inappropriate prescribing, 41.1% of them acknowledge unfamiliarity with chemotherapy regimen guidelines based on risk evaluation for FN, whereas 55.71% worried that neutropenia development might lead to delay in chemotherapy schedule [Figure 4].

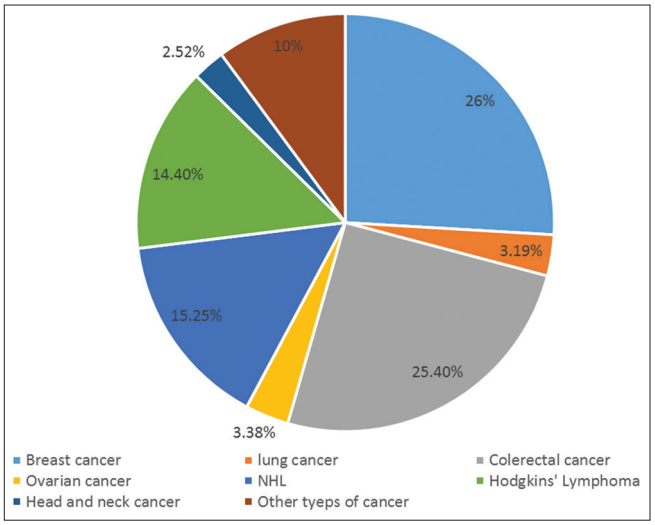

Figure 1: Patients distribution based on cancer type

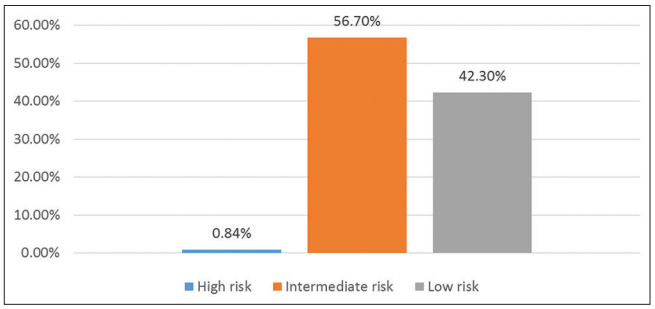

Figure 2: Percentage distribution of chemotherapy patients with febrile neutropenia

Economic burden due to inappropriate prescription of G-CSF

As shown in Figure 5, 61.70% of purchase cost of G-CSF was wasted due to its inappropriate prescribing [Figure 5]. The total expenditure on the purchase of G-CSF for all the recruited patients in this study was 187750 SAR, of which 115,850 were spent on the purchase of G-CSF that was inappropriately prescribed. The difference between the total amount spent and the money spent on inappropriate prescription of G-CSF was found to be statistically significant ($P < 0.05$).

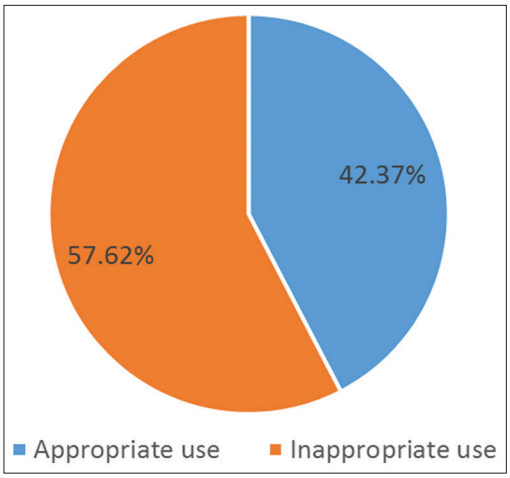

Figure 3: Appropriate and inappropriate use of granulocyte colony-stimulating factor

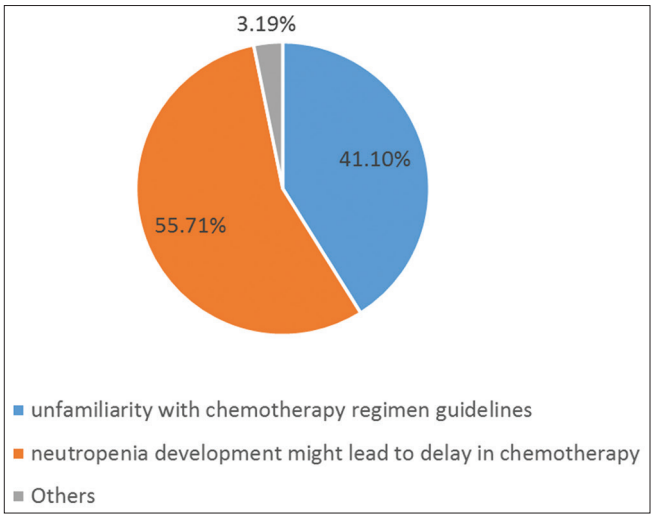

Figure 4: Reasons for inappropriate prescribing of granulocyte colony-stimulating factor

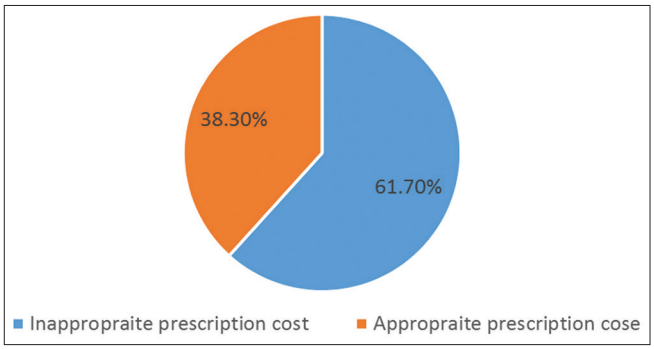

Figure 5: Cost analysis of inappropriate and appropriate prescription of granulocyte colony-stimulating factor

DISCUSSION

The prophylactic use of G-CSF has been shown to reduce the risk of FN and FN-mediated hospitalization in patients receiving cancer chemotherapy.[11] However, rational use of G-CSF in chemotherapy patients has to be promoted to reduce risk of causing thrombocytopenia[14] and other undesired manifestations of G-CSF in addition to unnecessarily increasing economic burden on the patients and their caregivers. Therefore, the use of G-CSF has to be promoted under regulations based on the ASCO guidelines and other published data. Our study exhibited a remarkably higher proportion of irrational G-CSF prescription at our location due to a self-proclaimed fear of delayed chemotherapeutic action on account of possible neutropenia.

A recent study carried out elsewhere in the Kingdom of Saudi Arabia[13] demonstrated a higher proportion of appropriate prescription of G-CSF, while studies carried out outside the Kingdom showed approximately 63–69% of the compliance with the prescription guidelines.[15,16] However, our study exhibited a lower percentage of compliance with the guidelines with only around 42% of the prescription adhered to the guidelines, whereas 58% received G-CSF inappropriately. Out of all appropriate prescribing pattern in our study, 34% of them were found in secondary prophylaxis with only 8% of them were in primary prophylaxis prescription. This indicates a rational pattern as physicians' are prescribing G-CSF after witnessing FN in the previous cycle. On the contrary, most of the inappropriate prescription was noted in primary prophylaxis due to a fear of neutropenia development during chemotherapy. This irrational approach is seen at higher level in our organization when compared to other studies as shown above. It is proposed to obviate this trend by developing hospital guidelines based on established guidelines and published literature with comprehensive details on risk factors for FN and when to prescribe G-CSF. Addition of G-CSFs to the chemotherapy protocol will high a significant impact in alleviating the inappropriate prescribing.[17]

The outcome of this study has limited claim as it does not resemble the actual prescribing errors in G-CSF across whole region or the country as the sample for this study was collected from a single location. Further, being a cross-sectional study, where the samples were collected during specific time and duration, a more comprehensive and long-term study could have highlighted more details on intraorganizational prescribing errors. Moreover, poor documentation made additional difficulty to determine the inappropriate use of G-CSF in intermediate cases.

Nevertheless, this study will lay the foundation stone for many more studies in the Kingdom of Saudi Arabia, and indeed, this is one the rare study done in this part of the world to evaluate the use of G-CSF prescribing pattern in Saudi Arabia.

CONCLUSION

Higher proportion of inappropriate prescriptions of G-CSF was noted in our hospital. Inadequate knowledge of the

chemotherapy risk of FN as well as perceived fear of possible induction of FN was documented as major reasons for inappropriate prescription of G-CSF. Health-care professionals including clinical pharmacists should play an active to improve G-CSF prescribing pattern. In addition, availability of comprehensive hospital guidelines may rationalize the therapeutic approach in G-CSF prescription.

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