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Granulocyte Colony-Stimulating Factor in Adults with Solid Tumors - Need for Implementing Guidelines

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Abbreviations:

CIFN: Chemotherapy-induced febrile neutropenia; GCSFs: Granulocyte colony-stimulating factor; ASCO: American Society of Clinical Oncology; GM-CSF: granulocyte-macrophage colony-stimulating factor; NCCN: National Comprehensive Cancer Network; FN: Febrile neutropenia; ANC: absolute neutrophil count; OS: Overall survival; RR: relative risk;

1. Abstract

1.1. Background: Chemotherapy-induced febrile neutropenia (CIFN) is a major dose-limiting toxicity associated with chemotherapy. It is associated with an overall hospitalization rate of 35% and an average mortality rate of 9.5% (2.6% -21.4%).

Granulocyte colony-stimulating factors (GCSFs) are often prescribed as primary or secondary prophylaxis to manage chemotherapy-induced febrile neutropenia (CIFN). American Society of Clinical Oncology (ASCO) guidelines exist to optimize the use of GCSFs.

The main aim was to quantify the inappropriate use of GCSFs in Primary and secondary prophylaxis and acute (CIFN) management using the ASCO of Clinical Oncology guidelines as a reference.

1.2. Methods: This retrospective cohort study included 408 randomly selected adult patients with solid tumors who received chemotherapy.

1.3. Results: A total of 408 patients were included. Overall, GCSFs were prescribed appropriately in 208 (51%) patients, and in 200 (49 %) were considered inappropriate.

The median duration of GCFs was 5 days in most patients.

1.4. Conclusions: Inappropriate use of GCSFs is common in terms of indications and duration in adult patients with solid tumors receiving chemotherapy. Adherence to the guidelines will optimize their use.

2. Background

Granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) are often prescribed as primary or secondary prophylaxis for patients with (CIFN). (G-CSFs) are hematopoietic hormones that promote the maturation and growth of myeloid cells. These factors are clinically used in various situations, including the treatment of cyclical or congenital neutropenia and CIFN. According to clinical trials, G-CSFs are indicated to enhance patient quality of life, reduce hospitalization and parenteral antibiotic use, and, subsequently, reduce total cost. The American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) guidelines were developed in 1994 and then updated. The latest ASCO guidelines can be found at: www.asco.org/guidelines/csf [1]. The updated recommendations for the use of G-CSFs are summarized as follows:

Primary prophylaxis: G-CSF administration for patients who are expected to have a 20% or greater risk of febrile neutropenia (CIFN) or a risk of febrile neutropenia between 10 and 20% with associated risk factors based on medical history, age, disease characteristics, and risk of myelotoxicity associated with chemotherapy [2].

Secondary prophylaxis: G-CSF administration should be proposed when a reduced dose or treatment delay may compromise disease outcome (mostly but not exclusively in the curative setting) [2, 3].

G-CSFs for management of FN as adjunctive therapy can be considered for patients at high risk for infection complications (e.g., hypotension, pneumonia, multi-organ dysfunction, fungal infection, or profound neutropenia (absolute neutrophil count (ANC) < 100 µL]) [2-4].

Growth factors should continue until the neutrophil count recovers to > 1000 cells/mm3 on two consecutive days [4].

When chemotherapy is used with palliative intention and the patient develops FN, dose reduction should be considered. Adding G-CSFs before considering dose reduction is also considered inappropriate as per the ASCO guidelines [4].

G-CSF administration should be initiated between 24 and 72 h after chemotherapy [5].

Inappropriate use of G-CSFs is common, and it has not been shown to improve outcomes in randomized control trials. It has the potential to add to the overall cost of healthcare and expose cancer patients to unnecessary additional adverse events such as fatigue, dizziness, bone pain, nausea, and fever [6, 7].

The main objective of this study was to evaluate the use of G-CSFs in adult patients with solid tumors undergoing chemotherapy and its appropriate use as primary/secondary prophylaxis and in cases of FN using different risk categories (low, intermediate, and high risk) for FN complications using the ASCO guidelines as a reference. In the setting of FN, prescribing G-CSFs in patients with intermediate-risk FN without comorbidity and low-risk FN was considered inappropriate, whereas the use of G-CSFs in high-risk patients was considered appropriate.

3. Methods

This retrospective cohort study was conducted at a tertiary care center. The study was approved by the Institutional Review Board (#15-274) of the constitution, and no consent form was needed as all patients' identification was removed to ensure patient confidentiality. A total of 408 patients with solid tumors who received GCSF between 30th of November 2020 and 31st of October 2022 were identified and selected randomly through the pharmacy computer system (Cortex). We took every 5th patient on the pharmacy list, and the patients were enrolled according to the inclusion and exclusion criteria.

Electronic charts were reviewed by the Department of Health Records (HIM) system. A data collection standard form was developed, with the following data: patient demographic details (sex, age, weight, etc.). Chemotherapy intent was classified as curative or palliative based on the assessment of malignancy type and stage. The dose, dosing intervals, duration of therapy, and ANC monitoring plan were analyzed.

Patients were reviewed for the risk of CIFN, which included a review of their history and chemotherapy regimen administered. Chemotherapeutics were categorized as inducing a high, intermediate, or low risk of FN if the overall chance of CIFN was more than 20%, 10-20% and less than 10%, respectively. Patients at high risk for CIFN are candidates for primary prophylaxis. Low and intermediate risk of CIFN and having risk factors were also considered as appropriate candidates for primary prophylaxis and shown in (Figure 1).

The main aim of this study was to determine the rate of inappropriate use of growth factors for all three indications. Any deviation from the ASCO of Clinical Oncology guidelines was considered inappropriate.

Inclusion Criteria

• In addition to being the fifth patient randomly selected from a list of all adult patients receiving chemotherapy for solid tumors diagnosed from 30th of November 2020 to 31st of October 2022 in whom growth factors were used.

Exclusion Criteria:

• Patients on G-CSFs for non-cancer indications.

• Pediatrics patients.

• Patients with hematological malignancy.

• Lymphomas were excluded as they were treated for hematological malignancies at KFMC.

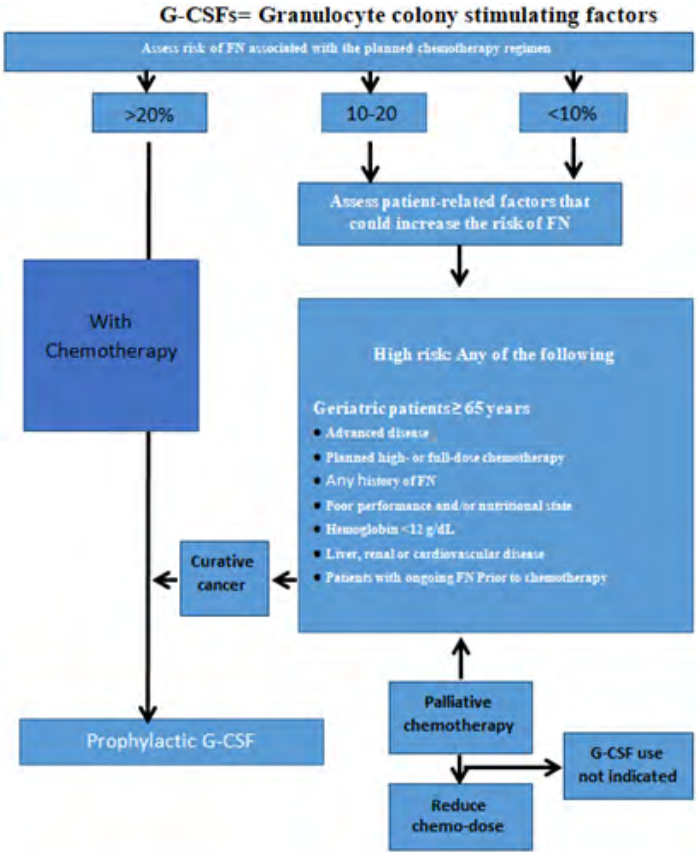

Figure 1a: ASC0 Guideline for G-CSFs initiation

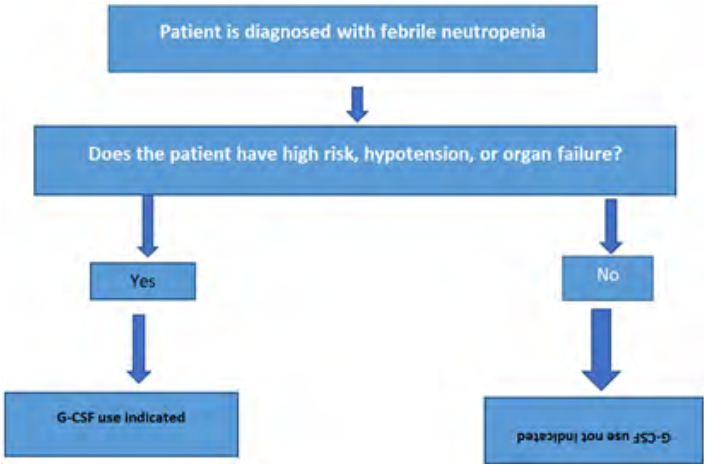

Figure 1b: ASC0 Guideline for Febrile neutropenia treatment with G-CSFs:

4. Statistics

Data were retrieved from the pharmacy electronic system, and from the chemotherapy sheets additional data from the HIM were necessary to determine whether the indication for G-CSF use in some patients was for primary/secondary prophylaxis or therapy of patients with established FN.

The data collected were quantitative, and statistical analyses were performed using SPSS version 21.

Nominal variables (all except age and G-CSF duration) are described using numbers and percentages. All variables were descriptive and measured by means of 'frequencies' function in order to determine the prevalence of a variable.

SPSS version 21 was used for descriptive statistics when summarizing the results for the appropriate use of the colony stimulation agent.

5. Results

Of the 665 patients with cancer who received G-CSFs, only 408 met the inclusion criteria (Figure 2). The solid tumors consisted mainly of breast, colorectal, and pancreatic cancers, representing 168(41.8%), 96 (23.5%), and 44 (10.9%), respectively. Most of the patients were women (n = 300, 73.5%), and the mean age was 50.5±12.8.

The risk categories of CIFN associated with chemotherapy were high (33.3%), intermediate (41.2%), and low (25.5%).

A total (312) patients received filgrastim at a dose of 300 µg/dose, and 48 patients received pegfilgrastim (Table 2). Filgrastim was administered for a median duration of 5 days. Overall, G-CSFs were prescribed appropriately in 208 (51%) patients in our study. G-CSFs were prescribed as primary prophylaxis in 220 (54%) cases, secondary prophylaxis in 168 (41%), and FN in 20 (5%) of our studied cases (Table 1).

The total number of inappropriate cases was 200/208 (49%) patients for all three indications (104, 84, and 12) in the primary, secondary prophylaxis, and acute management of CIFN, respectively (Table 1).

Of the 220 patients who received CSFs as primary prophylaxis, 104 represented (52%) of the total number of inappropriate cases. Seventy-two of the 104 patients had a moderate risk for febrile neutropenia (10-20%) based on the regimen used, but no additional risk factors were eligible for GCSFs, while 32 were at low risk for FN development but did receive G-CSFs (Figure 3).

One hundred and sixty-eight patients received G-CSFs as secondary prophylaxis, but only 84 patients were prescribed G-CSFs appropriately, whereas the other 84 patients were prescribed inappropriately. These patients represented 42% of the total inappropriate cases found in our study. The main reason for inappropriate use was that no dose reduction was considered before adding G-CSFs to chemotherapy used for non-curative disease purposes (palliative intent.

In 12 of 20 patients, G-CSFs were used in the treatment of FN, representing 6% of the total inappropriate cases (Table 1).

Duration and dosing of G-CSFs. Pegfilgrastim was used in 24% of the patients, and since it is a single fixed dose, all patients received it appropriately. The remainder received filgrastim; the duration ranged between 3 and 7 days, with the majority using it for 5 days (90%) of cases. None of the patients relied on the recovery of neutrophil counts on two consecutive days to guide therapy.

Therefore, despite the common practice of using filgrastim for five days. This was considered inappropriate according to study guidelines. This indicated that the majority of patients were in poor compliance with the ASCO guidelines regarding the duration of use.

These results are shown in table 2.

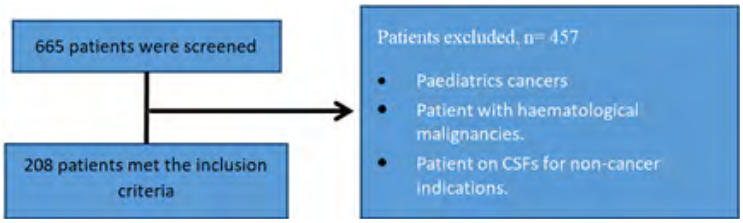

Figure 2: Patient enrollment flow chart.

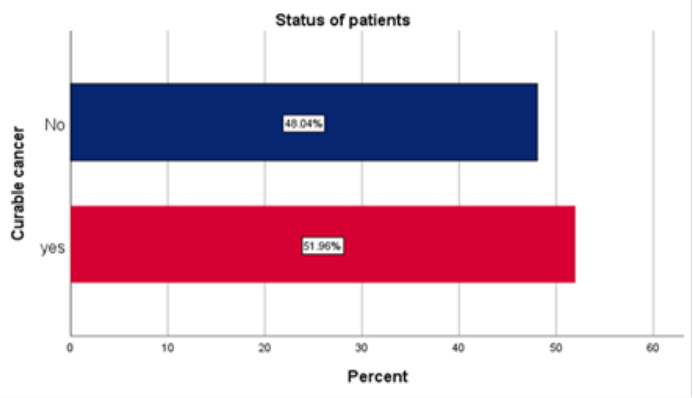

Figure 3: Distribution of patients according to curability of cancer.

Table 1: Baseline characteristic of the patients

Gender	Female: 300 (73.5 %)
	Male: 108 (26.5%)
Mean age	50.5±12.8
Type of cancer	Breast Cancer: 168 (41.2%)
	Colorectal Cancer: 72 (17.6%)
	Pancreatic cancer: 44 (10.8%)
	Rectal cancer: 28 (6.9%)
	Sarcoma: 12 (2.9%)
	Gastric cancer: 16 (3.9%)
Curable cancer:	212 (52%)
Type of chemotherapy	Primary prophylactic: 220 (53.9%) Appropriate: 116 (53%)
	Secondary prophylactic: 168 (41.2%) Appropriate: 84 (50%)
	Treatment of FN: 20 (4.9%) Appropriate: 8 (40%)

Table 2: Granulocyte colony-stimulating factor (G-CSF) used

Colony Stimulating Factor	No of patients (%)	Duration of therapy
Pegfilgrastin	96 (23.5%)	1 dose
Filgrastin	312 (76.47%)	7 days: 16 (5.12%)
		5 days: 220 (70.5%)
		4 days: 16 (5.12%)
		3 days: 60 (19.2%)

6. Discussion

CIFN remains a serious adverse event associated with chemotherapeutic agents and is associated with significant morbidity and mortality. In Singapore surveys, the mortality rate in post-chemotherapy FN ranged between 3% and 8.8%. [10]. Other studies have reported a hospitalization rate of 35% and mortality ranging from 2.6% to 22.4%, depending on coexisting morbidities [8-10].

Primary prophylaxis has the potential to improve the morbidity and mortality rates. In geriatric cancer patients (≥ 65 years old), retrospective, observational cohort study for patients who had chemotherapy and primary prophylaxis using G-CSF from January 2008 to August 2011 concluded that FN is prevalent among geriatric cancer patients receiving adjuvant chemotherapy despite G-CSF support especially with comorbidities.

The median overall survival (OS) rate was 6-12-months, and hazard ratios (HRs; unadjusted Cox model with 95% confidence intervals [CIs]) were estimated for patients receiving ≥1 dose of filgrastim, pegfilgrastim, or a placebo [11, 12].

Comparisons were performed using the log-rank test. A fixed-effect meta-analysis Filgrastim/Pegfilgrastim on OS in patients with lung cancer, the medium OS was 14.1 versus 11.1 months in patients receiving filgrastim (HR, 0.81; 95% CI 0.48-1.35; P = 0.412) [11].

Another meta-analysis of 148 trials of primary CSF prophylaxis in cancer patients also showed a significant decrease in the rates of documented neutropenic fever and infection [4].

A different meta-analysis including 61 randomized controlled trials (RCTs) comparing chemotherapy with or without G-CSF supportive therapy and reporting all-cause mortality within at least two years was significantly reduced. (relative risk [RR] 0.93, 95% CI 0.90-0.96) [13].

These data led to the widespread exponential use of G-CSFs in the management of neutropenic complications. However, these medications are not without their own side effects and add significantly to the cost of care if used inappropriately [14].

Guidelines have been developed and updated periodically to optimize the use of G-CSFS based on evidence. These guidelines have been adapted by different practices to optimize the use of growth factors. Limited real-world data address the inappropriate/overuse of these medications after implementing and adapting the guidelines by many practices.

Overutilization and underutilization are common. Our study primarily addressed the overutilization of G-CSFs. The study confirmed that G-CSFs are overutilized in patients with solid tumors undergoing chemotherapy in all clinical settings.

There was 51% compliance with the G-CSF prescription according to the ASCO guidelines for primary/secondary prophylaxis and therapy for FN. In other words, 49% (47%, 50%, and 40%) of G-CSF use was inappropriate according to the ASCO guidelines for the three indications. The study confirmed that G-CSFs are overutilized in patients with solid tumors undergoing chemotherapy in all clinical settings.

In primary prophylaxis, careful assessment of neutropenia risk can lead to avoidance of the use of G-CSF in low- and intermediate-risk individuals with no comorbidities, as per the ASCO of Clinical Oncology guidelines.

The MONITOR-GCSF observational study included 1447 evaluable patients from 140 cancer centers in 12 European countries treated with myelosuppressive chemotherapy. Patients were classified as under- (17.4%), correctly (56.6%), or over-prophylactic (26.0%) [15].

With regard to secondary prophylaxis, inappropriate use was common. In a Polish study, this was also highlighted, despite the knowledge among oncologists about the indication, highlighting the need to adhere to guidelines [16].

Alternative options for secondary prophylaxis include dose reductions, which can potentially reduce inappropriate utilization.

Our study indicates that the overuse of G-CSFs is common in FN settings. G-CSFs were administered to 10 patients in our study because of chemotherapy-induced neutropenia; 6 (60%) of them were inappropriately administered. These patients were stable and

did not require addition of growth factors. Although the numbers were small, there was a low threshold for potentially inappropriate use of G-CSFs in this setting. Treatment of neutropenia in patients with solid cancers who received chemotherapy. Filgrastim is considered appropriate in the presence of severe neutropenic symptoms, hypotension, or multiorgan failure.

Previous studies have shown that approximately 60%-65% of G-CSFs comply with prescribing guidelines for primary and secondary prophylaxis and management of Complicated FN [17].

According to the ASCO of Clinical Oncology guidelines, G-CSFS injection should be continued until the neutrophil count has recovered to > 1000 cells/mm3 on two consecutive days. In our study, the average use of G-CSFs was five days and was not guided by neutrophil counts in most cases. The duration was not an issue for pegfilgrastim, as it was used as a single dose [6].

Our study had several limitations. This was a retrospective review that included patients who had already received growth factors. This can potentially impact the underutilization or inappropriate omission of growth factors in primary prophylaxis secondary to febrile neutropenia. This may have an impact on the overall appropriate utilization of growth factors.

Our study also had a smaller number of patients included in the use of chemotherapy for curative intent, which can be partially explained by the study being conducted in a tertiary care center that receives patients who have failed first- and second-line therapies at other centers. The study also had an abundance of breast cancer and colorectal cancers, and this merely reflects the most common cancers seen in the studied population; therefore, in a different practice, these numbers may be different, and our results cannot be generalized to all community practices. Our study was also limited by the fact that it was a retrospective study conducted at one institution. Other guidelines, such as the EORTC and European guidelines, exist, and in our study, the ASCO guidelines were used as a reference. The impact of under-, over-, and appropriate utilization remains a subject of debate.

7. Conclusions

Despite the study limitations, we conclude that overutilization of GCSFs is common in all indications and may contribute to unnecessary side effects and increased cost of care.

Colony-stimulating factors are frequently overused or underused for the primary and secondary prevention and management of FN in adults with solid tumors receiving chemotherapy, despite the adaptation of the ASCO of Clinical Oncology guidelines.

8. Acknowledgment Section

• **Authors' contributions:** All authors contributed to the conceptual design of the study, data collection, analysis of the results, and mutual understanding of the conclusions.

S.M. Contribution to writing the abstract, statistical analysis, and manuscript. Contributed to data collection, data analysis, and manuscript review.

• **Author agreement:** All authors have approved the final version of this manuscript and warranted that this article is an original work, h has not received prior publication, and i is not considered for publication elsewhere.

• **Availability of data and materials:** All the data are available upon request.

• **Competing interests:** The authors have no conflicts of interest to declare.

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