

Filgrastim use: evaluation in cancer and critically ill non- cancer patients

Research Article

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Abbreviations: ANC, absolute neutrophil count; G-CSF, granulocyte colony-stimulating factors

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Summary

Since 1991, the benefits of using colony-stimulating factors (CSF) in cancer patients were evolving. They included preventing febrile neutropenia, decreasing its severity and duration, and reducing the risk of infection associated with dose intensive cancer chemotherapy. The American Society of Clinical Oncology (ASCO) guidelines summarize current data on the appropriate use of CSFs. If the rate of febrile neutropenia for a given combination chemotherapy regimen is <40%, routine prophylactic use of a CSF is not considered cost-effective and is not recommended by ASCO. In randomly selected patient population of 113 patients, filgrastim, a granulocyte CSF (G-CSF), use was evaluated. The following parameters including indications, dosage, route of administration, day of initiation, day of discontinuation, and absolute neutrophil count monitoring plan were evaluated for appropriateness based on ASCO guidelines. The results of this drug utilization review suggest a strong need for optimization of G-CSF use in our hospital setting. The major areas of optimization are: initiation and duration of G-CSF therapy, control of G-CSF use in febrile neutropenia, dosing, and the need for increasing the frequency of G-CSF use as prophylaxis.

I. Introduction

Filgrastim, a granulocyte colony-stimulating factor (G-CSF), is a hematopoietic hormone promoting the growth and maturation of myeloid cells, and in particular, the proliferation and differentiation of neutrophils (Valley, 2002). In 1991, filgrastim was marketed in the U.S to substantially reduce the duration and severity of neutropenia. Clinical trials have then indicated that CSFs enhanced patient quality of life, and reduced hospital costs (Hartmann et al, 1997; McQuaker et al, 1997; Ozer et al, 2000; Valley, 2002) by reducing the days of hospitalization and total number of days of treatment with parenteral antibiotics (Crawford et al, 1991; Valley et al, 2002). G-CSF has been safely administered in the prevention of infection as manifested by febrile neutropenia with non-myeloid malignancies, in drug-induced neutropenia for longer periods, in chemotherapy-induced neutropenia and in congenital and cyclic neutropenia (Hammond et al, 1989; Heard and Fink 1999). Also, filgrastim has been effective in intra-abdominal sepsis, neonatal sepsis, and pneumonia (Kollef, 1999; Bernstein et al, 2001; Khadaroo and Marshall, 2002).

To optimize CSF use, the American Society of Clinical Oncology (ASCO) adopted evidence-based guidelines in September 1994 (American Society of

Clinical Oncology, 1994). Since then, the guidelines were updated twice in March 1996 and in October 2000 (Ozer et al, 2000). A list of the relevant updated recommendations for the use of CSF are as follows:

1. Primary administration of CSF should be reserved for patients expected to experience a 40% or greater risk of febrile neutropenia; i.e., patients with compromised bone marrow, advanced cancer, advanced age, active infection, and/or open wounds.
2. Secondary prophylactic CSF administration can be considered in subsequent chemotherapy cycles of equal dose intensity if febrile neutropenia occurs with a prior cycle.
3. As adjunct to peripheral blood progenitor cell (PBPC) mobilization and post-transplantation, CSFs are effective. (A higher dose of G-CSF (10mcg/kg/day) in the setting of mobilization may be considered).
4. In established febrile neutropenia in certain high-risk patients (e.g., patients with pneumonia, hypotension, sepsis syndrome, multiorgan dysfunction, fungal infection, uncontrolled primary disease, or profound neutropenia (absolute neutrophil count (ANC) < 100/mcL), the use of CSFs together with antibiotics may be rational.
5. In patients with acute leukemia and myelodysplastic syndromes, G-CSF use is not

recommended before or during chemotherapy for priming effects; however, CSFs are recommended after completion of chemotherapy.

6. G-CSF administration in patients with acute lymphoblastic leukemia should begin after completion of the first few days of chemotherapy of the initial induction or first post-remission course, thus shortening the duration of neutropenia of less than 1000/mm³ by approximately one week.

7. In drug- induced neutropenia (e.g. neutropenic patients receiving pentamidine for treatment of pneumocystis pneumonia) CSF shall be considered, as well.

CSF dosing, initiation, duration, and ANC monitoring are among other issues addressed by the ASCO guidelines.

The objective of this study was to assess the extent of compliance of G-CSF use with the ASCO guidelines.

II. Materials and methods

The study was conducted in a 430-bed university hospital with inpatient and out-patient care services, including a PBPC transplant unit. A total of 113 patients who received G-CSF between February 1999 and May 2003 were identified and selected randomly through the pharmacy computer system. The charts were retrieved from the department of health records. Included in the study were medical records with complete and sufficient data for cancer patients and those with autologous PBPC donation and other causes of neutropenia (neonatal sepsis, pneumonia, and septic shock). Outpatients and neutropenic HIV patients were excluded from the study.

A data collection standard form was developed, pre-tested, and modified prior to including the following data: Patient demographic details (ID number, gender, age, weight, etc), prescribing data for the use of filgrastim (cancer and critically ill non-cancer patients), admitting diagnosis, and units of admission. Chemotherapy intent was classified as curative or palliative based on the assessment of the malignancy type and its stage. Dose, dosing interval, duration of therapy, route of administration, ANC monitoring plan, and major adverse effects were also included.

Results were recorded and analyzed using a database system (SPSS). Microsoft Excel was used to produce related figures.

Drug use was evaluated for appropriateness based on whether ASCO guidelines were adopted.

III. Results

A. Patient characteristics:

Oncology patients accounted for 92%, whereas the remaining applied to intensive care unit patients. The median patient age was 39.5 years (range: 0– 85). Female subjects constituted 47.3% and 32% were of the pediatric age.

The patient diagnosis as well as the type of malignancy in cancer patients is listed in **Table 1**. A total of 173 courses of chemotherapy and radiation therapy were administered to 113 patients. Out of 173 G-CSF courses, 137 were thoroughly followed and included in the study. The goals of chemotherapy and radiation therapy

were curative in 66% courses and palliative in 34% courses. Only 10% of G-CSF courses were started on inpatient basis but continued on outpatient basis. Outpatient prescriptions for G-CSF were excluded from the study.

B. Indications

The majority of patients (81) were admitted for febrile neutropenia. Approximately 62% of G-CSF courses were administered to patients with established febrile neutropenia or pancytopenia following chemo and/or radiotherapy (**Table 2**). Five patients received G-CSF for PBPC mobilization and post infusion support. Also 22.5% and 19% of G-CSF courses were for primary and secondary prophylaxis, respectively. Twelve episodes of febrile neutropenia requiring hospitalization occurred while patients were receiving G-CSF for primary or secondary prophylaxis. In all cases, G-CSF was continued during hospitalization.

Table 1. Patient Diagnoses.

Diagnosis	No. Patients n =113 (%)	No. G-CSF courses n =173 (%)
Breast cancer	3 (2.6)	4 (2.3)
Kidney tumor	3(2.6)	3 (1.7)
Neutropenia of premature birth/ Neonatal sepsis / Drug-induced cancer/ Aplastic anemia	3(2.6)	4 (2.3)
Acute lymphoblastic leukemia	8 (7.1)	14 (8.1)
Acute myeloid leukemia	16 (14.1)	32 (18.5)
Nonhodgkin's lymphoma	13 (11.5)	19 (11)
Metastatic pancreatic cancer	4 (3.5)	5 (3)
Hodgkin's disease	3 (2.6)	3 (1.7)
Neuroblastoma	4 (3.5)	6 (3.5)
Multiple myeloma	2 (1.8)	4 (2.3)
Non small-cell lung cancer	6 (5.3)	8 (4.6)
Burkitt lymphoma	6 (5.3)	8 (4.6)
Sarcoma	17 (15)	29 (16.7)
Germ cell and pineal gland tumor	1 (0.9)	1 (0.6)
Medulloblastoma	1 (0.9)	1 (0.6)
Hairy cell leukemia	1 (0.9)	1 (0.6)
Septic shock /Acute respiratory syndrome/ Pneumonia/ Multi organ dysfunction	3 (2.6)	6 (3.5)
Metastatic colon carcinoma	2 (1.8)	2 (1.2)
Waldenström's macroglobulinemia	1 (0.9)	1 (0.6)
Astrocytoma	1 (0.9)	1 (0.6)
Myelodysplasia / Anemia	1 (0.9)	1 (0.6)
Retinoblastoma	2 (1.8)	6 (3.5)
Squamous cell carcinoma	2 (1.8)	3 (1.7)
Spindle cell carcinoma	1 (0.9)	1 (0.6)
Ovarian cancer	1 (0.9)	1 (0.6)
Chronic lymphoblastic leukemia	1 (0.9)	1 (0.6)
Gastric adenocarcinoma	1 (0.9)	2 (1.2)
Metastatic rectal carcinoma	1 (0.9)	1 (0.6)
Mantle cell lymphoma	2 (1.8)	2 (1.2)
Non small cell lung cancer	1 (0.9)	1 (0.6)
Cholangiocarcinoma	1 (0.9)	1 (0.6)
Glioma multiforme (occipital)	1 (0.9)	1 (0.6)

Moreover, in 60% of febrile neutropenic patients, one or more high risk factor (pneumonia, sepsis, hypotension, multiorgan dysfunction, fungal infection, $ANC < 100/mm^3$) was concomitantly present (Figure 1).

C. Reported adverse effects of G-CSF

Bone pain was reported in nineteen (16.5%) patients receiving G-CSF. In one patient, G-CSF use was associated twice with maculopopular rash necessitating discontinuation of the drug and replacement with a granulocyte macrophage CSF.

D. Dosing

Only in 4 patients, G-CSF was prescribed for intravenous administration because of a profound

unresponsive pancytopenia associated with sepsis and pneumonia. However, G-CSF was prescribed for daily subcutaneous administration in 109 patients. The usual prescribed dose was 5 mcg/kg/day. In 24 patients, doses were increased by 5 mcg/kg/day according to the duration and severity of neutropenia. In 5 patients, 5 mcg/kg of G-CSF were given three times daily. For peripheral blood progenitor cell collection (n=4) and post-infusion support, the dose of G-CSF was 10 mcg/kg/day. A total of 101 (74%) G-CSF courses were rounded to a G-CSF vial size (300 mcg). The thirty-three courses not rounded to a vial size were dosed exactly at 5 or 10 mcg/kg. In 40 courses, the doses were 210 mcg. In these instances, several doses were obtained from a single vial. Doses < 5 mcg/kg/day are listed in Table 3.

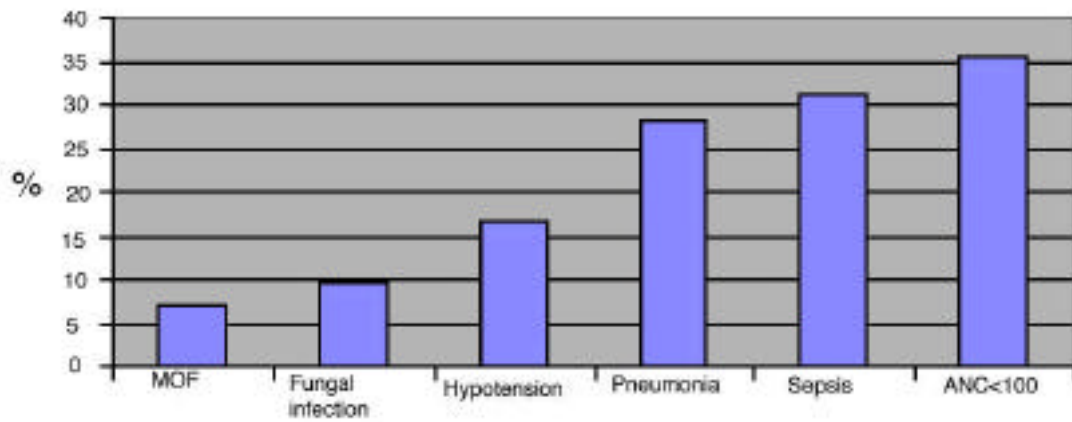


Figure 1. Risk factors justifying the use of G-CSF in febrile neutropenia according to ASCO guidelines. (MOF: Multiorgan dysfunction; ANC: Absolute neutrophil count).

Table 2. Indications for G-CSF courses.

Indications	No. of G-CSF courses n ^a (%)
Primary prophylaxis	31 (17)
Secondary prophylaxis	26 (14)
Peripheral blood progenitor cell mobilization	4 (2)
Following peripheral blood progenitor cell infusion	4 (2)
Established febrile neutropenia post radiation	6 (3)
Established febrile neutropenia post chemotherapy	59 (32)
Sepsis syndrome/ Drug-induced cancer/ Pneumonia/ Febrile neutropenia/ Neutropenia of premature birth	12 (6)
Post induction chemotherapy in acute lymphoblastic leukemia	4 (2)
Post consolidation chemotherapy in acute myeloid leukemia	5 (3)
Chemotherapy induced a febrile neutropenia or pancytopenia	20 (11)
Aplastic anemia	4 (2)
Inappropriate indications	11(6)

^a one G-CSF course could be used for more than one of the above mentioned indications. (n=186)

Table 3. Discrepancies between calculated G-CSF doses per body weight and actual administered doses (Underdosing).

Discrepancy	No. G-CSF courses (n=66)
(-) < 6%	13
(-) 10% - 17%	29
(-) 20% - 27%	18
(-) 30% - 46%	6

E. Initiation and Duration

The initiation of G-CSF is described for almost all G-CSF courses (Table 4). As for prophylactic G-CSF courses 77% were initiated 24 hours after the last dose of chemotherapy. The rest started 48 hours post chemotherapy. Approximately 42.5% of prophylactic G-CSF courses were initiated following chemotherapy of one to two day duration, 29% following three-day duration chemotherapy and 16% following chemotherapy of five-day duration. Three patients were given G-CSF 24 hours before starting chemotherapy cycle because they were found to have neutropenia (based on ANC readings) upon admission. The mean duration of G-CSF therapy was 4.8 days (range: 1-25 days).

F. Monitoring and Discontinuation

Absolute neutrophil count values at day of G-CSF initiation are shown in Figure 2. In 35 courses, ANC was far less than 200/mm³ when G-CSF was initiated. Inpatients' ANCs were monitored on a daily basis in 96% of cases. Among 137 G-CSF courses, 126 had ANC results documented on the day of discontinuation, or even two days following discontinuation while 10 courses were continued on an outpatient basis. ANC values at day of G-CSF discontinuation are shown in Figure 3.

IV. Discussion

A few studies have evaluated the use of G-CSF. In a multi-center drug utilization review, a total of 31% and 49% of G-CSF use were proven to be inappropriate with respect to the indication and dose, respectively (Yim et al, 1995). Another study, conducted to assess the use of G-

CSF by mailing surveys to oncologists, indicated that the majority of G-CSF use was similar to that recommended by the ASCO guidelines, except that most physicians chose to use G-CSFs for the treatment of febrile neutropenia, an indication not supported by ASCO guidelines (Bennett et al, 1996). A total of 35% of physicians described discontinuing CSFs with an ANC of 4999/mm³ and 65% with ANC of 9999/mm³. In addition, Baker et al, (2000) conducted a drug utilization evaluation on G-CSF use in cancer patients. 65% of G-CSF courses in their study were prescribed for primary prophylaxis. Of these, 74% followed chemotherapy in patients with an expected incidence of febrile neutropenia 40%. They found that the greatest departure from the ASCO guidelines included aspects of initiation and discontinuation of G-CSF courses and inadequate documentation of ANC recovery.

Our drug utilization review emphasized on whether G-CSF multiuse at a 430 bed hospital was compliant with 2000 the ASCO guidelines.

The majority (88%) of prophylactic G-CSF courses were appropriately prescribed. In some cases, G-CSF administration followed a dose-intensive chemotherapy with an expected incidence of febrile neutropenia of >40% like sarcomas, non-Hodgkin's lymphoma, Burkitt lymphoma, acute myeloid leukemia and acute lymphoblastic leukemia (Manero and Kantarjian, 2000; Ozer et al, 2000, Holdsworth , 2001). Some courses followed chemotherapy in patients with compromised bone marrow reserve secondary to extensive prior chemo- or radiotherapy, with poor performance status and more advanced cancer, or patients with advanced age.

Table 4. Day of G-CSF initiation in patients receiving chemotherapy. ^a

Duration of Chemotherapy (No of days)	Day of G-CSF initiation									
	-1	0	1	2	3	4	5	6	7	8
1	3	-	-	17	1	2	3	-	-	-
2	-	-	-	-	4	-	-	-	-	-
3	-	-	-	-	-	13	4	1	-	-
4	-	-	-	-	-	-	3	-	-	-
5	-	-	-	-	-	-	-	10	-	1
6	-	-	-	-	-	-	-	-	1	-

^a The G-CSF uses for established febrile neutropenia were not included in this table.



Figure 2. ANC at day of G-CSF initiation.

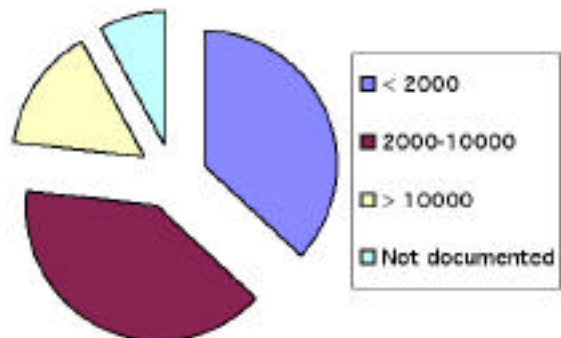


Figure 3. ANC at day of G-CSF discontinuation

As for G-CSF courses that followed chemotherapy cycles for prophylaxis, G-CSF dosage reductions could improve patient convenience and decrease the cost of the treatment.

In addition, the use of G-CSF post-induction chemotherapy in acute lymphoblastic leukemia and post-consolidation chemotherapy in acute myeloid leukemia in 7 of our patients has been recommended by the updated 2000 evidence based ASCO guidelines (Ozer et al, 2000).

The use of G-CSF for established cases of febrile neutropenia demonstrated a strong need for improvement (Berghmans, 2002). Approximately 77 % of our G-CSF courses were for established febrile neutropenia and chemotherapy induced established pancytopenia. As much as 80% of febrile neutropenia cancer patients did not receive G-CSF prophylaxis post-chemotherapy, which demonstrated a gap in the strategy followed in the Oncology unit to prevent neutropenic fever.

A small percentage (9%) of the courses were indicated for critically ill non-cancer patients but presenting with either septic shock, drug-induced cancer, pneumonia, neutropenia of premature birth, multiorgan failure, or drug-induced aplastic anemia.

The ASCO guidelines recommend that CSFs may be warranted in high risk patients with febrile neutropenia with certain prognostic factors, such as pneumonia, hypotension, multiorgan dysfunction, sepsis syndrome, fungal infection or $ANC < 100/mm^3$ (Ozer et al, 2000). However, only forty-two studied patients with febrile neutropenia had the above-mentioned prognostic factors warranting CSF use. This implied an abuse of G-CSF in some reviewed cases of febrile neutropenia.

G-CSF was administered to 12 patients who developed febrile neutropenia despite prophylactic administration of G-CSF. The ASCO guidelines do not tackle the benefit of continuing CSFs during febrile neutropenia episodes among patients receiving prophylaxis (Ozer et al, 2000). On the other hand, it was difficult to deduce from our results whether continuing CSFs when febrile neutropenia occurred translated into a reduction in antibiotic use or days of hospitalization.

The use of G-CSF for peripheral blood progenitor cell mobilization collection in 3% of the courses is warranted by the ASCO guidelines. Note that we considered G-CSF use in 8% of courses deserve further analysis, inappropriate according to the strict criteria defined by ASCO guidelines (Ozer et al, 2000).

Although G-CSF is a safe drug, it has two major disadvantages: its high cost and its side effects. Medullary bone pain, a common incidence (Lacy et al, 2002), was reported in 16.5% of our reviewed records. On the other hand, severe maculopapular rash which is a rare side effect of G-CSF, was reported in only one patient requiring discontinuation of the drug (Lacy et al, 2002).

Most prescribed G-CSF doses at the study site followed ASCO recommendations, yet low dose regimens ($< 5 \text{ mcg/kg/d}$) were included in 48% of courses. Although some studies have shown that lower doses are effective (Eguchi et al, 1989), more evidence is needed to support

its routine use. As much as 74% of G-CSF courses were rounded to a G-CSF vial size (300 mcg) to enhance patient convenience and reduce costs without compromising clinical response.

As for initiating CSFs compared to ASCO guidelines, at least 53 doses in our patient sample would have been eliminated if G-CSF use were started at 48-72 hours rather than 24 hours after chemotherapy regimens of three days or less while retaining efficacy. In 93% of our reviewed "more than 3 day" chemotherapy regimens, patients received prophylactic G-CSF 24 hours after the last dose of chemotherapeutic agent. According to ASCO recommendations, G-CSF should be started 24 hours after chemotherapy administration in patients receiving chemotherapy regimens lasting more than 4 days to avoid possibility of therapeutic failure. In 3 patients, G-CSF therapy was initiated 24 hours before chemotherapy cycle because they were found to be leukopenic upon admission, neglecting the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy (Lacy et al, 2002).

Note that $ANC > 1000/mm^3$ and $platelets > 100000/mm^3$ are two conditions allowing for initiating a dose-intensified chemotherapy. Although studies have investigated optimal schedules for administering G-CSF (Ribas et al, 1996; Soda and Kanda, 1996), in our study, daily ANC monitoring was recorded for all hospitalized patients during each course of G-CSF therapy. However, in patients who were discharged on G-CSF, it was impossible to monitor ANC because outpatients were excluded from our study. To evaluate CSF response, the ASCO guidelines (McQuaker et al, 1997; Ozer et al, 2000) recommend assessing a response to GSFs by obtaining ANCs twice weekly and documenting the neutrophil nadir, as well as the recovery. ANC parameters, and the predicted time for neutrophil recovery following the nadir should determine the duration of G-CSF therapy. Since the timing of neutrophil nadir varies among patients, ANC remains the most reliable parameter defining the duration of G-CSF therapy.

In our patient sample, the mean duration of G-CSF therapy was 5 days. However, the range was very wide (1-25 days) because in 36 out of 137 G-CSF courses, G-CSF was used for prolonged febrile neutropenia. In our study, most of G-CSF administration as prophylaxis lasted less than seven days. Comparable to previous studies, this finding needs further evaluation to assess clinicians' compliance in using the neutrophil nadir and recovery as endpoints of CSF therapy.

In established febrile neutropenia, discontinuation of G-CSF administration is mainly based on ANC monitoring; consequently, earlier discontinuation of G-CSF and decreasing cost while maintaining effectiveness would result (Crawford et al, 1992).

In this review study, 77% G-CSF courses were discontinued with an $ANC < 10000 \text{ cells/mm}^3$, while 14% of courses achieved $ANC > 10000 \text{ cells/mm}^3$. Moreover, 8% of evaluated G-CSF courses did not have an ANC recorded within 48 hours of discontinuation of G-CSF.

One way to minimize laboratory costs for daily ANC monitoring in future chemotherapy cycles where G-CSF will be prescribed for primary or secondary prophylaxis is to frequently monitor and document ANC in initial cycles potentially projecting the number of G-CSF doses required (Baker and McCune, 2000; Valley, 2002).

It is evident that health care practitioners should improve G-CSF use at the hospital setting and facilitate cost-effective therapy. Based on this review, a better ANC monitoring, and a decrease in chemotherapy dosage in palliative therapy, as an alternative to G-CSF use should be adopted. Practitioners should remind not to prescribe G-CSF in febrile neutropenia except when associated with the above-mentioned prognostic factors (Figure 1). In addition, initiation of CSF therapy 48-72 hours rather than 24 hours following chemotherapy regimens of three days or less is recommended. Also, G-CSF as prophylaxis could be optimized and included more frequently in future chemotherapy cycles to prevent frequent and fatal episodes of febrile neutropenia.

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