Maximizing the Outcomes in Cancer Patients Receiving Chemotherapy Through Optimal Use of Colony-Stimulating Factor

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ABSTRACT

OBJECTIVE: To discuss clinical data on the utility of 2 colony-stimulating factors (CSFs), filgrastim and pegfilgrastim, in reducing the risk and incidence of neutropenic complications with chemotherapy.

DATA SOURCES: This article reviews the data from the clinical studies for both pegfilgrastim and filgrastim. Additionally, data from large, population-based retrospective analyses on the clinical and economic consequences of chemotherapy-induced neutropenia (CIN) are reviewed.

CONCLUSIONS: CIN remains an undertreated condition despite the evidence of its danger. Pivotal trials show that CSFs like pegfilgrastim and filgrastim are safe and effective in reducing both the incidence and duration of CIN and febrile neutropenia in patients who have been treated with myelosuppressive chemotherapy. Approximately 11 daily injections of filgrastim per chemotherapy cycle are required to achieve this clinical end point. Pegfilgrastim provides all the clinical benefits of daily filgrastim for managing CIN with a single dose per chemotherapy cycle.

KEYWORDS: Colony-stimulating factor, Chemotherapy-induced neutropenia, Chemotherapy, Filgrastim, Pegfilgrastim

Chemotherapy-induced neutropenia (CIN) is a serious and frequent side effect of cancer chemotherapy. As the absolute neutrophil count (ANC) drops in the days after chemotherapy, the risk of infection increases.¹ Patients with CIN may not show the typical signs of infection since neutrophils are effectors of the inflammatory response; fever may be the only indicator. Since infection in a patient with neutropenia can be rapidly life-threatening, fever with neutropenia, or febrile neutropenia (FN), is treated as a medical emergency, typically with hospitalization and the prompt administration of intravenous antibiotics.

Patients treated with myelosuppressive chemotherapy routinely experience neutropenia and its complications during their treatment. When CIN occurs, the subsequent cycles of chemotherapy may be delayed to allow for ANC recovery, or the chemotherapy doses may be reduced in an effort to minimize the incidence of CIN in later cycles. Using practice pattern data (collected between 1993 and 2000) Link and colleagues investigated chemotherapy dose delivery in patients with breast cancer and noted that there was at least one chemotherapy dose delay or reduction in nearly half of the patients (45%).² Such dose delays and dose reductions may compromise the effectiveness of treatment in patients with potentially curable malignancies such as breast cancer and non-Hodgkin's lymphoma (NHL). Studies in these 2 tumor types have identified a dose-response relationship, with higher chemotherapy dose intensity (RDI $\geq 85\%$ in breast cancer, RDI $>75\%$ in NHL) being associated with improved patient survival.³⁻⁵

Chemotherapy-induced neutropenia and FN may also have substantial economic impact on health care resources. The costs of hospitalization for CIN are high and may be even greater in older patients.^{6,7} Kuderer and colleagues analyzed hospital-admission data from the University HealthSystem Consortium database for the years 1995 through 2000 and found that the average cost of admissions was approximately \$19,369 per hospitalization (\$12,302 for solid tumors, \$27,340 for hematologic malignancies).⁷ Thus, reducing the incidence of CIN has the potential to save the health care system significant economic resources.

The clinical and economic impacts of CIN and FN may be reduced by supportive therapy with hematopoietic colony-stimulating factors (CSFs) that stimulate the growth and differentiation of neutrophils. The current clinical practice guidelines of the American Society of Clinical Oncology (ASCO) for the use of CSFs recommend a "watch and wait" approach unless the chemotherapy regimen is associated with a risk of FN of 40% or higher, or the patient has one of the special circumstances outlined by ASCO.⁸ Unless these criteria are met, the guidelines recommend that prophylactic growth factors not be used until an episode of FN has occurred and thus "proved" the need for growth factors. Unfortunately, this "watch and wait" approach can result in dose delays and reductions, which can have serious consequences in

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patients with potentially curable malignancies.

Delivering standard-dose chemotherapy on time is particularly important in elderly patients, who are at higher risk for hospitalization for FN than younger patients (odds ratio 2.17; 95%CI, 1.43-3.30; $P < 0.05$), and in whom dose reduction is associated with poorer outcomes.^{9,10} Accordingly, the National Comprehensive Cancer Network recommends the routine use of growth factor support, starting in cycle 1, in older patients who are treated with myelosuppressive chemotherapy.¹¹

Filgrastim and pegfilgrastim are CSFs designed to decrease the incidence of infection, as manifested by FN, in patients with non-myeloid malignancies treated with myelosuppressive anticancer drugs.^{12,13} Filgrastim is administered as a daily injection throughout the expected ANC nadir, until the ANC has recovered to at least $10 \times 10^9/L$, the recommended end point in therapy with colony-stimulating factors.¹² Pegfilgrastim, used once per chemotherapy cycle, is administered as a single, fixed-dose injection.¹³ This article reviews the clinical data on filgrastim and pegfilgrastim. The data show that when these CSFs are used appropriately, they are effective in reducing the risks and incidence of neutropenic complications.

Clinical Impact of Granulocyte Colony-Stimulating Factors

Filgrastim

Filgrastim was approved by the U.S. Food and Drug Administration (FDA) in 1991 and has since been used in approximately 3.5 million patients. Filgrastim is indicated to decrease the incidence of infection, as manifested by FN, in patients with non-myeloid malignancies treated with myelosuppressive anticancer drugs. Based on data submitted to the FDA, the following dosing recommendations were made:

Filgrastim should be administered no sooner than 24 hours after the administration of cytotoxic chemotherapy and should be administered daily for up to 14 days, until the ANC has reached $10 \times 10^9/L$ after its expected nadir.¹²

The elimination half-life of filgrastim in healthy subjects and patients with cancer is approximately 3.5 hours, which necessitates daily dosing. Owing to the short serum half-life of the drug, the serum levels of filgrastim fluctuate with daily dosing.

One of the reasons for administering filgrastim to an ANC of at least $10 \times 10^9/L$ is that the ANC can decrease by approximately 50% within the first 48 hours after the discontinuation of daily dosing.¹⁴ Thus, stopping earlier may put the patient at greater risk of FN and related negative sequelae.

The safety and efficacy of filgrastim were evaluated in 2 similar phase 3 trials, one conducted in the United States¹⁵ and the other in Europe.¹⁶ Patients with small-cell lung cancer were randomized to either filgrastim or placebo daily, starting 24 hours after the completion of chemotherapy cycle 1 and continuing in each cycle. Filgrastim and placebo were given for a maximum of 14 days or until a postnadir ANC of $10 \times 10^9/L$. Cyclophosphamide and doxorubicin were administered on

FIGURE 1 Effect of Filgrastim on the ANC in Cycle 1 of Chemotherapy in the Pivotal U.S. Trial

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FIGURE 2 Clinical End Points in the Pivotal Trials of Filgrastim

Data from references 15 and 16.

day 1 only with etoposide given on days 1, 2, and 3.

Filgrastim significantly reduced the severity and duration of CIN (Figure 1), with an earlier ANC nadir, shorter median duration of severe neutropenia (DSN) (3 versus 6 days; $P < 0.001$), and a faster recovery of the ANC to its prechemotherapy value.¹⁵ The number of days of severe neutropenia in a cycle was also substantially less with filgrastim (median, 1 versus 6 days). Filgrastim was effective over all 6 cycles.

Data on the clinical end points in both pivotal trials are shown in Figure 2. The incidence of first-cycle FN and the overall incidence of FN were approximately 50% less with filgrastim in both studies.^{15,16} Patients were treated with filgrastim for approximately 11 days to achieve these outcomes.^{15,17} Hospitalization rates and the use of intravenous antibiotics were significantly less with filgrastim (37% versus 58%; $P < 0.02$, and 39% versus 58%; $P < 0.04$, respectively) in the European trial.¹⁶ The rates of culture-confirmed infections were less in the filgrastim arms in both trials, but the differences were not significant.

Dosing inconsistent with that specified in the prescribing infor-

FIGURE 3 Mean DSN in Cycle 1 in the Pivotal Trials of Pegfilgrastim

Data from references 20 and 21.

TABLE 1 Number of Injections of Colony-Stimulating Factor Necessary to Achieve Clinical End Points in Clinical Studies

Investigators	Filgrastim	Placebo
Crawford et al. ¹⁵ (phase 3)	11 (median)	—
Trillet-Lenoir et al. ¹⁶ (phase 3)	9-14	—
	Filgrastim	Pegfilgrastim
Holmes et al. ²⁰ (phase 3)	11 (mean)	1
Green et al. ²¹ (phase 3)	11 (median, cycle 1) 11 (median, cycle 2) 11 (median, cycle 3) 10 (median, cycle 4)	1 1 1 1
Holmes et al. ²³ (phase 2)	11 (mean)	1
Vose et al. ²⁴ (phase 2)	11 (median)	1

mation for filgrastim may produce suboptimal outcomes. The start of filgrastim therapy has been delayed in clinical practice due to the potential inconvenience of daily injections and cost constraints. Koumakis and colleagues have shown that both the incidence of FN and the total duration of filgrastim therapy increase when the administration of filgrastim after chemotherapy is delayed.¹⁸ When filgrastim was given 24 hours after high-dose cyclophosphamide, the incidence of FN was 16%, and it was administered for an average of 11.5 days. When filgrastim was initiated at 96 hours, the rate of FN increased to 66%, and 15.5 days of therapy was required. Delaying filgrastim administration to more than 72 hours after chemotherapy was shown to result in more febrile episodes, antibiotic use, and higher cost.

In summary, supportive care with filgrastim significantly reduced the DSN, decreased the rate of FN and length of stay by 50%, and also decreased the use of intravenous antibiotics and the duration of their use. On average, 11 days of filgrastim support was necessary to achieve these benefits. These are important clinical measures in patients treated with myelosuppressive chemotherapy, and the appropriate use of filgrastim produces optimal outcomes.

Pegfilgrastim

Pegfilgrastim is created by the covalent attachment of a 20-kd polyethylene glycol (PEG) moiety to the N-terminal of filgrastim. Filgrastim is cleared from the body by 2 mechanisms: neutrophil-mediated clearance and excretion by the kidneys.¹⁹ The greater size of the pegfilgrastim molecule due to the addition of the PEG moiety impedes renal clearance, resulting in the longer half-life of pegfilgrastim. Neutrophil-mediated clearance is, therefore, the major route of elimination of pegfilgrastim. However, this route is less active in neutropenic patients, in whom mature neutrophils have been depleted. As the neutrophil count recovers, the elimination of pegfilgrastim is accelerated. Consequently, this self-regulated clearance mechanism allows pegfilgrastim to remain in the body during periods of neutropenia and clears it from the body upon ANC recovery. This neutrophil-mediated clearance enables treatment with a single dose of pegfilgrastim per chemotherapy cycle.

The safety and efficacy of pegfilgrastim were shown in 2 similar double-blind randomized phase 3 trials, one conducted in the United States²⁰ and the other primarily in Europe.²¹ All patients had breast cancer and were treated with up to 4 cycles of adjuvant chemotherapy with doxorubicin and docetaxel. Patients were randomized to a single dose of pegfilgrastim per chemotherapy cycle (6-mg fixed dose in the European study, 100-μg/kg weight-based dose in the U.S. study) or filgrastim (5 μg/kg/d to an ANC >10 × 10⁹/L or for 14 days, whichever came first). The study drugs were started 24 hours after the completion of the chemotherapy and were continued in each subsequent chemotherapy cycle.

Data on the primary end point in these trials are shown in Figure 3. A single dose of pegfilgrastim given once per chemotherapy cycle shortened the DSN as effectively as daily filgrastim. The U.S. study found that the mean DSN in cycle 1 was 1.8 days with filgrastim and 1.7 days with pegfilgrastim; in the European study it was 1.6 days with filgrastim and 1.8 days with pegfilgrastim. The rates of FN across all chemotherapy cycles in both studies ranged from approximately 10% to 20%. The rate with pegfilgrastim and filgrastim was 13% versus 20% in the European trial and 9% versus 18% ($P < 0.05$) in the U.S. trial.

Misset et al. have reported that similar chemotherapy regimens result in a 100% rate of severe neutropenia in the absence of growth factor, with a mean duration of neutropenia of 5 to 7 days and an incidence of FN of 30% to 40%.²²

Thus, pegfilgrastim provides protection from CIN and FN comparable to that with filgrastim with only one dose per chemotherapy cycle.

Duration of Therapy With Filgrastim and Pegfilgrastim

The number of injections of filgrastim necessary to achieve the desired clinical end points is shown in Table 1. The clinical benefits of filgrastim relative to placebo were well established in 2 phase 3 trials, which show that optimal benefits are achieved when filgrastim is initiated 24 hours after chemotherapy and continued until the ANC has reached $10 \times 10^9/L$ after its expected nadir. This required approximately 11 daily injections of filgrastim.^{15,16} Similarly, in the 4 pegfilgrastim trials, a single dose of pegfilgrastim per chemotherapy cycle was compared with daily filgrastim. As shown in Table 1, these studies established that a single dose of pegfilgrastim produces outcomes comparable to those with 11 doses of filgrastim.^{20,21,23,24}

Meza and colleagues conducted a combined analysis of the data from the 2 pivotal pegfilgrastim trials. They determined the time to ANC recovery and the number of filgrastim injections administered in these trials. They found that by days 12 to 14, 90% of patients who had been given filgrastim had a postnadir ANC of $10 \times 10^9/L$, the recommended end point in therapy with colony-stimulating factors.²⁵ A median time to ANC $\geq 10 \times 10^9/L$ was 11 days in all cycles, and the median time to ANC $\geq 2 \times 10^9/L$ was only 1 to 2 days less.

Conclusions

Filgrastim and pegfilgrastim are safe and effective in ameliorating CIN, the major dose-limiting toxicity of chemotherapy. Nonetheless, as evidenced in the literature, patients continue to be hospitalized for FN and to be given a lower than intended chemotherapy dose, even though maintaining the dose intensity is known to correlate with optimal clinical outcomes in certain types of cancers. The costs of treating FN and its clinical sequelae are substantial, both to patients and to the health care system.

The reasons for these suboptimal outcomes may be reactive "watch and wait" use (not using growth factor support prophylactically when it is indicated), not administering the complete course of growth factors, and delaying the initiation of growth factors.

The clinical trials for filgrastim and pegfilgrastim have shown that these CSFs significantly reduced the incidence of first-cycle FN and the overall incidence of FN, as well as the DSN, length of stay, and the use of intravenous antibiotics. Pegfilgrastim provides all the clinical benefits of daily filgrastim for CIN with a single dose per chemotherapy-cycle, replacing approximately 11 injections of filgrastim per cycle. It is possible that with this simplified once-per-chemotherapy-cycle dosing regimen for pegfilgrastim, more patients may be able to achieve positive clinical outcomes.

DISCLOSURES

Author John W. Mucenski is on speakers bureaus of Amgen, Aventis, Merck, and OrthoBiotech and on the advisory boards of Amgen, Aventis, and Genentech, with compensation. Mucenski served as principal author of this study. Critical revision of the manuscript and analysis and interpretation of data were the work of Mucenski and author Jeffrey E. Shogan.

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