Granulocyte Colony-Stimulating Factor Use in Patients With Chemotherapy-Induced Neutropenia:

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Neutropenia is the primary dose-limiting toxicity in patients treated with myelosuppressive chemotherapy, leading in some cases to substantial morbidity and early mortality, and disrupting treatment with potentially curative regimens. The use of granulocyte colony-stimulating factors (G-CSFs) such as filgrastim (Neupogen) and pegfilgrastim (Neulasta), as primary prophylaxis starting in the first cycle of chemotherapy, has been shown to reduce the rates of febrile neutropenia (FN) and of FN-related hospitalization, as well as the use of intravenous anti-infectives. A recent meta-analysis has shown significantly lower infection-related mortality with the first-cycle use of G-CSFs. Both filgrastim and pegfilgrastim were originally approved on the basis of their effectiveness in patients treated with chemotherapy regimens that are associated with a 40% or greater risk of FN. Pegfilgrastim, which is given once per cycle, has been shown to reduce the risk of FN by 94% in breast cancer patients treated with docetaxel (Taxotere). In addition, a recent cost-minimization analysis has shown that first-cycle use of pegfilgrastim may be cost-neutral in patients in whom the predicted risk of FN is less than 20%. These findings have important implications for clinical guidelines for preventing chemotherapy-induced neutropenia and FN.

Chemotherapy-induced neutropenia (CIN) is the primary dose-limiting toxicity in patients with cancer treated with systemic myelosuppressive agents. The most serious manifestation of neutropenia, febrile neutropenia (FN), which may be a sign of life-threatening infection, particularly in patients who are frail or elderly and in those with comorbidities.[1] It frequently necessitates chemotherapy dose reductions and delays, which have been shown to compromise the efficacy of some chemotherapy regimens.[2-4] In addition, CIN and FN have negative effects on patients’ quality of life (QOL), an outcome that is getting more attention in the treatment of cancer.[5,6] Because the risk of CIN and FN is greatest in the first cycle of chemotherapy,[7] appropriate supportive care should be initiated in the first cycle in patients who are at increased risk to minimize the effects of neutropenia and its complications.

The proactive use of the granulocyte colony-stimulating factors (G-CSFs) filgrastim (Neupogen) and pegfilgrastim (Neulasta) can reduce the incidence, severity, and duration of neutropenia and its complications. Filgrastim, which was approved by the US Food and Drug Administration (FDA) in 1991, is given daily in weight-based doses.[8] Pegfilgrastim, a G-CSF that was bioengineered to have a sustained duration of action and was approved in 2002, is given once per cycle in a fixed dose.[9] Both filgrastim and pegfilgrastim were FDA approved on the basis of their efficacy in decreasing the risk of FN in patients with cancer who were treated with highly myelosuppressive chemotherapy regimens (rates of FN of ≥ 40%).[10-13] The results of more recent studies support the efficacy[14] and cost-effectiveness[15] of pegfilgrastim given in the first cycle with chemotherapy regimens with which the risk of FN is less than 20%. In this article, I review the clinical and economic benefits of initiating filgrastim and pegfilgrastim in the first cycle of chemotherapy.

**Pivotal Trials of Filgrastim**

Filgrastim was approved for managing CIN on the basis of the results in two multicenter trials in patients with small-cell lung cancer who were treated with cyclophosphamide (Cytoxan, Neosar), doxorubicin, and etoposide, a regimen associated with a risk of FN of about 60%.[10,11] Patients in both studies were randomized to filgrastim 4 to 8 µg/kg or to placebo on days 4 through 17 after the chemotherapy (the filgrastim could be discontinued if the postnadir absolute neutrophil count [ANC] exceeded 10 × 10^9/L after day 12). The primary end point was the incidence of FN, defined as a temperature ≥ 38.2°C and ANC < 1.0 × 10^9/L.
In both studies, the incidence of FN was lower by about 50% with filgrastim.[10,11] In one of them, the incidence was 77% in the placebo group and 40% in the filgrastim group ($P < .001$)[10]; in the other, it was 53% and 26% ($P < .002$), respectively.[11] Furthermore, filgrastim also significantly reduced the incidence of culture-confirmed infections; the incidence and duration of grade 4 neutropenia (ANC < 0.5 x 10^9/L); the number of days of intravenous (IV) antibiotic use or the proportion of patients treated with IV antibiotics; and the number of days of hospitalization or the proportion of patients hospitalized. The only adverse event that was attributed to filgrastim was mild-to-moderate musculoskeletal pain, which was not dose-limiting.

**Pivotal Trials of Pegfilgrastim**

The approval by the FDA of pegfilgrastim for prevention of CIN was based on the results of two large randomized controlled trials in patients with breast cancer who were treated with doxorubicin and docetaxel (Taxotere).[12,13] a regimen that is associated with an FN rate of 38% in patients with breast cancer when it is used without growth factors.[14]

The trials were similar in design and investigated whether pegfilgrastim was as effective as filgrastim in managing CIN. Patients were randomized to a single injection of pegfilgrastim per chemotherapy cycle followed by daily injections of placebo, or to daily injections of filgrastim 5 µg/kg. The pegfilgrastim was given as a weight-based dose (100 µg/kg) in one of the studies[12] and as a fixed dose (6 mg) in the other.[13] Treatment began on day 2 of each cycle, about 24 hours after the chemotherapy. The filgrastim or placebo injections were continued for 14 days or until the ANC was at least 10 x 10^9/L after the nadir.

A single dose of pegfilgrastim was at least as effective as daily filgrastim in both trials. The incidence and duration of grade 4 neutropenia were similar with both agents in all cycles, and the agents were comparable in terms of the depth of the ANC nadir and the time to neutrophil recovery. There were no differences in safety. The trials were not designed to detect this effect, but in both, the incidence of FN (temperature ≥ 38.2°C and ANC < 0.5 x 10^9/L) was lower with pegfilgrastim (Figure 1), and in one of them, the difference was significant ($P = .029$).[12] Retrospective analysis of pooled data from these studies showed that treatment with both filgrastim and pegfilgrastim helped make it possible to give the planned doses of chemotherapy on time.[15] At least 90% of the patients in both groups were treated with an average relative dose intensity (RDI) of 85% or higher. Both studies also showed that the efficacy of the G-CSFs was greater in the later cycles, with the incidence of grade 4 neutropenia being lower in cycles 2 through 4 than in cycle 1 (Figure 2a).[12,13] One of the studies also reported that the duration of grade 4 neutropenia in cycles 2 through 4 was significantly shorter with pegfilgrastim than with filgrastim (Figure 2b).[12]
A more recent pivotal trial has shown that pegfilgrastim as primary prophylaxis also has clinical benefits when it is given with a less toxic moderately myelosuppressive regimen.[16] This randomized, multicenter, multinational, double-blinded study was conducted in 928 patients with breast cancer treated with single-agent docetaxel, 100 mg/m² every 3 weeks, a regimen that has been associated with FN rates of 10% to 20% in the absence of CSFs.[17,18] The patients were randomized to pegfilgrastim 6 mg or placebo once per cycle, given approximately 24 hours after the chemotherapy. Patients in whom FN developed were treated with open-label pegfilgrastim in the following cycles. The primary end point was the incidence of FN, defined as in the other pivotal trials of pegfilgrastim.

The overall incidence of FN was 94% lower in patients randomized to pegfilgrastim than in those randomized to placebo, and the rates of FN-related hospitalization and use of IV anti-infectives were also significantly lower with pegfilgrastim (all \( P < .001 \)) (Figure 3). Full-dose chemotherapy was given on schedule in similar proportions of patients (pegfilgrastim 80% and placebo 78%). This was expected, because the study design specified that patients in either group in whom FN developed be switched to open-label pegfilgrastim. It should also be noted that a greater proportion of patients in the placebo group were switched to open-label pegfilgrastim (19% vs 2%). There were two deaths due to infection-related complications in the placebo group but none in the pegfilgrastim group.

Regimens Requiring Routine G-CSF Support to Maintain Dose and Schedule

Filgrastim is given routinely starting in the first cycle in dose-dense (q14d) chemotherapy regimens, which have emerged as a standard-of-care regimen in node-positive early-stage breast cancer on the basis of the results of Cancer and Leukemia Group B (CALGB) 9741 trial.[19,20] The first studies with dose-dense regimens used filgrastim support, and later studies have reported that once-per-cycle pegfilgrastim in place of filgrastim is also safe and effective in q14d regimens in patients with breast cancer,[21,22] non-Hodgkin's lymphoma (NHL),[23] Hodgkin disease,[24] and small-cell lung cancer.[25] For example, FN occurred in 2 (1.5%) of 135 patients treated with dose-dense concurrent doxorubicin and cyclophosphamide followed by paclitaxel (AC-T) with pegfilgrastim support—a rate comparable to or lower than that achieved with filgrastim given on days 3 through 10 of each cycle.[21]

The routine use of G-CSFs starting in the first cycle is also recommended with the docetaxel, doxorubicin, and cyclophosphamide (TAC) regimen—another emerging standard-of-care adjuvant regimen in breast cancer.[26] Routine use of first- and subsequent-cycle G-CSF with TAC has been shown to substantially reduce the rates of FN and other adverse events, as well as to mitigate the effects of the chemotherapy on patient QOL. In an interim analysis of safety in the Spanish Breast Cancer Research Group (GEICAM) 9805 study, a trial of TAC vs fluorouracil (5-FU), doxorubicin, and
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Cyclophosphamide (FAC) in which an early protocol amendment mandated the use of G-CSFs in the first cycle of TAC, the rates of FN were 23.8% in the 109 patients treated with TAC alone and 3.5% in the 114 patients given G-CSF in the first cycle.27 In addition, the rate of other grade 3 and 4 adverse events was 50% in patients treated with TAC alone but only 20% in those who were also given G-CSF.

A later analysis of QOL in this study found that the decrements in QOL in the 416 patients who were given G-CSF in the first cycle were similar to those in the 520 patients who were treated with FAC and that the decrements in QOL were significantly greater (P = .008) in the 114 patients who were treated with TAC alone.[28] Analysis of data in this larger group of patients also showed significantly lower rates of FN, grades 3 and 4 diarrhea, severe asthenia, and grades 2, 3, and 4 mucositis in patients treated with TAC plus first-cycle G-CSF than in those treated with TAC alone.

Broader Confirmation of Clinical Benefits of G-CSF
Two meta-analyses have confirmed that first-cycle use of G-CSF reduces the risk of neutropenia and its complications in adult patients with solid tumors or malignant lymphoma who are treated with myelosuppressive chemotherapy. Both analyses were of controlled trials in which patients were randomized to G-CSF starting in the first cycle or to placebo or no treatment. The first meta-analysis, published in 2002,[29] was of eight randomized controlled trials (N = 1,144) of filgrastim or lenograstim (a glycosylated recombinant G-CSF [Granocyte]), including the two pivotal trials of filgrastim.[10,11] Across the broad range of malignancies and chemotherapy regimens studied, the incidence of FN was 62% lower with G-CSF (P = .001) and the incidence of documented infections was 49% lower (P = .001).

A more recent meta-analysis[30] pooled the results of the same eight trials and those of six other trials in which G-CSF was started in the first cycle, including the most recent pivotal trial of pegfilgrastim.[16] (The first two pivotal trials of pegfilgrastim[12,13] were ineligible for this meta-analysis because they used an active control, filgrastim.) The 3,091 patients had been treated with systemic chemotherapy for a wide variety of tumor types, including NHL, breast cancer, lung cancer, sarcoma, and testicular cancer. The meta-analysis found that FN was 46% less common in the G-CSF group than in the control group (20% vs 37%, P < .001). The G-CSF was beneficial regardless of the type of disease (NHL vs solid tumor) or the age of the patient population (elderly vs all ages). This meta-analysis also found significantly lower infection-related mortality in the patients given first-cycle G-CSF (1.75% vs 3.3%) (P < .001).[30] This later meta-analysis also confirmed that treatment with G-CSF helps make it possible to give the chemotherapy at full dose and on schedule. The average RDI was 94.5% in the G-CSF group and 88% in the control group (P < .001).[30] This finding is particularly important in light of the evidence that giving chemotherapy at full dose and on schedule is associated with greater long-term disease-free and overall survival.[2-4,19,31-33]

Preliminary results from FIRST, a fully enrolled community-based study, also suggest that G-CSF initiated in the first cycle of chemotherapy markedly reduces the incidence of neutropenia and its complications. This prospective open-label study was conducted in patients with cancers other than leukemia or myelodysplastic syndromes who were given pegfilgrastim in the first and subsequent cycles of myelosuppressive chemotherapy. At the time of an interim analysis of data on 874 patients, FN had occurred in just 2% of patients during cycle 1 and in 3% in cycles 1 and 2 combined.[34] The rate of neutropenia- or FN-related hospitalization was 2% in cycles 1 and 2, and of antibiotic use was 5%. Serious adverse events thought to be related to the use of pegfilgrastim occurred in only three patients (0.3%).
Mild-to-moderate bone pain that is usually well managed with nonnarcotic analgesics is the only adverse event that has consistently been reported with the use of filgrastim and pegfilgrastim. The incidence of bone pain and other musculoskeletal complications in the meta-analysis discussed above was 12% in the control groups and 22% in the G-CSF groups.[30] Filgrastim and pegfilgrastim are associated with a similar incidence of bone pain. Retrospective analysis of data from the pivotal trials of pegfilgrastim that used filgrastim as the active control found no significant differences in the incidence, severity, or duration of bone pain with the two agents.[35] Severe bone pain that is related to metastasis from prostate, breast, and other types of cancer is common, but there is no evidence that the use of G-CSFs may exacerbate it.[35] It may not be possible in the advanced disease setting to distinguish bone pain from metastases or other disease-related causes from that associated with G-CSF. Nonnarcotic analgesics were used in 37% of the patients treated with pegfilgrastim and in 31% of those treated with placebo who had bone pain in the study by Vogel and colleagues, and narcotic analgesics were used in 10% and 9%.[16] Most of the reported bone pain was mild or moderate in severity, occurring in 27% of the placebo group and in 31% of the patients who received pegfilgrastim.[16]

Primary G-CSF Prophylaxis: Economic Considerations

It is reasonable to expect that first-cycle G-CSF has not only clinical benefits but also economic benefits. The cost-neutral risk threshold (the point at which the cost of primary G-CSF prophylaxis is offset by the reduction in FN-related medical costs) can be determined by analyzing data on the costs of hospitalization for FN and on the efficacy of G-CSF in reducing the rates of FN and hospitalization.

The earliest cost analysis of filgrastim was published in 1993, and the assumptions about the efficacy of G-CSF, the probability of hospitalization for FN, and the likely length of stay were based on data from the first pivotal trial of filgrastim.[36] The model showed that first-cycle use was cost-neutral in patients in whom the risk of FN, on the basis of the chemotherapy regimen, was ≥ 40%, in those who had been hospitalized with FN during treatment with the same regimen, and in those who were considered at increased risk of FN because of advanced age, severe debilitation, or other medical complications.[36] On the basis of these findings, the current guidelines of the American Society of Clinical Oncology recommend the proactive use of CSF when the chemotherapy-related risk of FN is 40% or greater or when patients are at high risk of FN because of special circumstances.[37]

The cost-minimization model was updated 5 years later to incorporate more inclusive cost data from the same hospital, including data on the cost of nursing care, the laboratory, the blood bank, radiology, respiratory care, and other support services.[38] The estimated cost of hospitalization increased substantially, leading to a marked change in the risk threshold. The proactive use of G-CSF was cost-neutral when the chemotherapy regimen was associated with an FN risk of approximately 23%.

It should be noted that the two cost models discussed above included only the cost of the growth factors, the cost of their administration, and certain costs in patients who were hospitalized with FN, including charges for the room, antibiotics, fluids and tubing, and professional fees, and used data
from a single center. Another update of the model also incorporated indirect costs of FN (eg, time lost from work, lower productivity while at work, and time spent by caregivers assisting the patient) as well as direct costs that had not been captured in the earlier versions of the model (eg, outpatient visits, emergency department visits, home healthcare visits, laboratory tests, prescription and over-the-counter drugs, and medical devices).[39] After these additional costs had been added, the risk threshold for the cost-effective first-cycle use of G-CSF decreased to between 18% and 22%. A new cost-minimization analysis with pegfilgrastim, rather than filgrastim, has recently been reported.[40] The clinical factors in this model were determined on the basis of the results in the meta-analysis of 14 randomized controlled clinical trials of G-CSF[30] and the most recent pivotal trial of pegfilgrastim.[16] Accordingly, the baseline assumptions were that the risk of FN with chemotherapy was 20% and the risk of FN was 94% lower in patients who were treated with pegfilgrastim than in those who were not. Under these conditions, there was a net cost-saving with pegfilgrastim when the risk of FN was greater than 15%. The first-cycle use of pegfilgrastim should therefore be considered not only because of its clinical benefits, which have been shown in clinical trials and meta-analysis, but also because of its economic benefits in patients treated with moderately myelosuppressive regimens.

Conclusions

A growing body of clinical data support the first-cycle use of filgrastim and pegfilgrastim to reduce the rates of FN, FN-associated hospitalizations, and FN-related use of IV anti-infectives; to help maintain the RDI of the chemotherapy; and to mitigate the effects of chemotherapy on patients’ QOL. Recent studies have shown that pegfilgrastim reduces the rates of FN in patients who are treated with moderately myelosuppressive chemotherapy regimens and that its use is cost-neutral when the expected rate of FN is as low as 15%. These findings have important implications for guidelines for prevention of CIN and FN.

Disclosures:

Dr Rader has received honoraria from Amgen.

References:


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