

Myeloid Growth Factor Therapy for Prophylaxis of Febrile Neutropenia in Non-Myeloid Malignancies: Appropriate Doses and Schedules

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Key Words

Myeloid growth factors, febrile neutropenia, chemotherapy, non-myeloid malignancy

Abstract

Myeloid growth factors (MGFs) are used for the prophylaxis of febrile neutropenia and maintenance of scheduled dose delivery in the treatment of patients undergoing cancer chemotherapy. To spare cost and for patient convenience, in adults MGFs are used at schedules, doses, and durations that differ from the approved prescribing information of the U.S. Food and Drug Administration. These variations include rounding doses to convenient sizes, fewer days of treatment, a shorter interval between cycles, and same-day administration with chemotherapy. Some of these variations are supported by clinical trial results and practice guidelines. (*JNCCN* 2007;5:229–234)

In 1991, the U.S. Food and Drug Administration (FDA) approved filgrastim, the first myeloid growth factor (MGF), for decreasing the incidence of infection in patients with non-myeloid malignancies. Two additional approved myeloid growth factors are currently available, sargramostim (1991) and pegfilgrastim (2002; Table 1). To spare cost and for patient convenience, the MGFs are used at schedules, doses, and durations that differ from the approved product labeling. This article focuses on the

doses and schedules used for the indications included in the National Comprehensive Cancer Center Network (NCCN) Myeloid Growth Factors Clinical Practice Guidelines in Oncology (to view the most recent version of these and other NCCN guidelines, visit <http://www.nccn.org>).¹ These indications include prophylaxis of febrile neutropenia and maintenance of scheduled dose delivery in the treatment of adults undergoing cancer chemotherapy for non-myeloid malignancies. This article does not address doses and schedules of MGFs in children, myeloid malignancies, stem cell mobilization, stem cell transplant, or cyclic neutropenia.

FDA-Approved Indications, Doses, and Schedules

Filgrastim

Filgrastim is a human granulocyte colony-stimulating factor (G-CSF).²

Indications: Filgrastim is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever.

Dose for Cancer Patients Undergoing Myelosuppressive Chemotherapy: The recommended starting dose of filgrastim is 5 mcg/kg/d. Doses may be increased in increments of 5 mcg/kg for each chemotherapy cycle, according to the duration and severity of the absolute neutrophil count (ANC) nadir. (Note: This incremental dosing is not common in clinical practice.)

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Table 1 Myeloid Growth Factors Approved by the FDA

Available Agents
Filgrastim (Neupogen®)
Sargramostim (Leukine®)
Pegfilgrastim (Neulasta®)

Schedule: Filgrastim should be administered no earlier than 24 hours after the administration of cytotoxic chemotherapy. Filgrastim should not be administered in the 24 hour period before administration of chemotherapy.

Duration: Filgrastim should be administered daily for up to 2 weeks, until the ANC has reached 10,000/mm³ following the expected chemotherapy-induced neutrophil nadir. The duration of filgrastim therapy needed to attenuate chemotherapy-induced neutropenia may be dependent on the myelosuppressive potential of the chemotherapy regimen employed. Filgrastim therapy should be discontinued if the ANC surpasses 10,000/mm³ after the expected chemotherapy-induced neutrophil nadir.

Sargramostim

Sargramostim is a recombinant human granulocyte-macrophage colony-stimulating factor.³

Indication: Sargramostim is not FDA approved for prophylaxis of febrile neutropenia in nonmyeloid malignancies. The following is based on the FDA approved indication for neutrophil recovery following chemotherapy for acute myeloid leukemia (AML).

Dose: There is not an FDA approved dose for this indication. The dose for neutrophil recovery following chemotherapy for AML is 250 mcg/m². This is the dosing recommended in the NCCN and ASCO guidelines.^{1,4}

Schedule: For neutrophil recovery following chemotherapy for AML, sargramostim is started on day 11 or 4 days following the completion of induction chemotherapy.

Duration: For neutrophil recovery following chemotherapy for AML, continue until the ANC is more than 1500 cells/mm³ for 3 consecutive days or a maximum of 42 days.

Pegfilgrastim

Pegfilgrastim is a covalent conjugate of G-CSF and monomethoxypolyethylene glycol.⁸

Indications: Pegfilgrastim is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia.

Dose: Pegfilgrastim, 6 mg, is administered once per chemotherapy cycle.

Schedule: Pegfilgrastim should not be administered in the period 14 days before and 24 hours after administration of cytotoxic chemotherapy.

Duration: One dose of pegfilgrastim is administered per chemotherapy cycle.

Variations

Doses: Approved doses for filgrastim and sargramostim are based on body size. Filgrastim is available in 300 mcg and 480 mcg dosage units. Sargramostim is available in 250 mcg and 500 mcg dosages. Rounding the dose to the nearest dosage unit or vial size is common and accepted practice for convenience and to decrease waste.^{1,4}

Pegfilgrastim is a fixed dose of 6 mg and is available in a 6-mg single-use syringe. Studies evaluating pegfilgrastim doses at 30 mcg/kg, 100 mcg/kg, and 300 mcg/kg have shown a neutrophil response.⁶ The 100-mcg/kg dose is closest to the approved dose of 6 mg. If a patient experiences hyperleukocytosis (white blood cell counts > 100 × 10⁹/L) from the 6-mg dose, a reduced dose would probably provide protection from febrile neutropenia or be useful in maintaining scheduled chemotherapy dose delivery while avoiding unacceptable toxicity. However, because the drug is available only in a set 6-mg dose, dose reduction is not practical and is not recommended. A nonpegylated MGF could be considered for subsequent cycles.

Filgrastim and Sargramostim Duration: The duration of filgrastim, recommended by the FDA-approved prescribing information, is daily for up to 2 weeks, until the ANC has reached 10,000/mm³ after the expected chemotherapy-induced neutrophil nadir. Variations on this schedule are seen in practice and published in guidelines. NCCN recommendations are to initiate the MGF daily beginning within 1 to 3 days after completion of chemotherapy until post-nadir ANC recovery returns to normal or near-normal ANC levels according to laboratory standards.¹ The American Society of Clinical Oncology (ASCO) guidelines recommend starting the MGF 24 to 72 hours after the

administration of myelotoxic chemotherapy, and continuing until an ANC of at least 2 to $3 \times 10^9/L$ is reached. The 2006 European Organisation for Research and Treatment of Cancer guidelines do not address the schedule or duration of MGF administration.⁷

In a retrospective medical record review of the use of filgrastim in intermediate-grade non-Hodgkin lymphoma (NHL) treated with first-line CHOP chemotherapy (cyclophosphamide, adriamycin, vincristine, prednisone) at 12 sites in the United States, Scott et al.⁸ suggest a lower incidence of febrile neutropenia may be associated with a longer duration of filgrastim prophylaxis (a mean of 4.7 days of prophylaxis vs. a mean of 10.1 days). A study by Weycker et al.⁹ reviewed data obtained from the medical claims processing system of a large U.S. health plan. The subjects were patients who had claims for chemotherapy and a diagnosis of NHL, breast cancer, or lung cancer. They reported that the likelihood of hospitalization for neutropenia or infection declined with each additional day of filgrastim prophylaxis. They found that the mean duration of filgrastim prophylaxis ranged from 4 to 7 days, and that shorter (vs. longer) courses of prophylaxis were associated with increased risks for hospitalization in patients with NHL and breast cancer.⁹

Patients on the Cancer and Leukemia Group B 9741 dose-dense chemotherapy schedule were treated with filgrastim on days 3 through 10 (7 doses) each cycle, with low rates of febrile neutropenia or dose delays.¹⁰

Papaldo et al.¹¹ reported the study results of 5 different schedules of G-CSF tested in 5 consecutive cohorts of early breast cancer patients treated with epirubicin and cyclophosphamide in a non-randomized study design. The G-CSF schedules were: 480 mcg/d subcutaneously days 8 to 14; 480 mcg/day on days 8, 10, 12, and 14; 300 mcg/d on days 8 to 14; 300 mcg/d on days 8, 10, 12, and 14; and 300 mcg/d on days 8 and 12. The schedule that used G-CSF on 2 days only (days 8 and 12) was equivalent to the other schedules with respect to incidence of grade 3 and 4 neutropenia, rate of fever episodes, incidence of fever episodes, incidence of neutropenic fever, need for antibiotics, and percentage of delayed cycles. As discussed in the ASCO 2006 guidelines, these results suggest that less frequent dosing might provide equal efficacy with fewer side effects and less cost. However, the study was observational, non-randomized, and under-powered in a population of patients who would not undergo MGF

support under the current guidelines. Djulbegovic et al.¹² cautioned that a change in practice of filgrastim scheduling should be based on randomized clinical trials.

Variations on duration of filgrastim use within a chemotherapy cycle range from 2 doses given 4 days apart as per Papaldo et al.,¹¹ to the suggestion that some patients may experience improved outcomes when the duration more closely matches the prescribing information. NCCN and ASCO guidelines have chosen a middle course between these schedules. **Pegfilgrastim Schedule:** The pivotal trials leading to FDA approval support the use of pegfilgrastim for chemotherapy regimens given every 3 weeks.⁴ The prescribing information for pegfilgrastim states it should not be given more frequently than every 14 days.⁴ The pharmacokinetics of pegfilgrastim predict its usefulness for every-2-week cycles of chemotherapy. The elimination of pegfilgrastim is self-regulated by neutrophil receptor-mediated clearance.

Johnston et al.⁶ reported pharmacokinetic data from a randomized dose-escalation trial of pegfilgrastim in 13 patients receiving paclitaxel and carboplatin for lung cancer. The results show that pegfilgrastim levels had returned close to baseline by day 12. The authors predict that the use of pegfilgrastim for every-2-week chemotherapy cycles will not result in enhanced marrow toxicity.

Yang et al.¹³ conducted a retrospective analysis of pegfilgrastim levels and ANC from 6 clinical trials of patients undergoing myelosuppressive chemotherapy for various tumor types, including lung cancer, breast cancer, NHL, and Hodgkin lymphoma. The authors found that by day 12, only 1 of 87 patients had a pegfilgrastim level greater than the EC_{20} . The EC_{20} value was defined as the lowest pegfilgrastim concentration able to elicit meaningful granulopoiesis. The authors concluded that by day 12, pegfilgrastim levels in most patients would be too low to stimulate neutrophils, and also that by the time the patient's neutrophils are high enough to be treated with the next cycle of chemotherapy, the neutrophils are also high enough to provide effective clearance of pegfilgrastim, further protecting against the unintended simultaneous stimulation of granulopoiesis and exposure to chemotherapy.

Variations on the scheduling of pegfilgrastim to accommodate a dose-dense schedule have been published. These variations require giving chemotherapy sooner than 14 days from the last dose of pegfilgrastim.

Studies in patients undergoing dose-dense chemotherapy also provide evidence for safety and efficacy on this schedule.

Burstein et al.¹⁴ described the use of pegfilgrastim as hematopoietic support for dose-dense every-2-week adjuvant breast cancer chemotherapy consisting of doxorubicin and cyclophosphamide for 4 cycles, followed by paclitaxel for 4 cycles. They concluded that pegfilgrastim could be safely and effectively substituted for short-acting filgrastim in this chemotherapy regimen. However, they found that during paclitaxel therapy the mean day-1 ANC ranged from 11,480 to 16,120. The investigators hypothesized the increase in ANC was caused by oral dexamethasone used for paclitaxel premedication. They reported that patients receiving no oral dexamethasone had a more normal day-1 ANC. It seems reasonable to ask if patients could more successfully receive short-acting filgrastim during the paclitaxel cycles, but the study did not address this question.

Wolff et al.¹⁵ reported 3 cases of patients experiencing myeloid toxicity after the use of pegfilgrastim for dose-dense every-2-week chemotherapy for breast cancer. Patient 1 was hospitalized for symptomatic hyperleukocytosis 48 hours after her second dose of paclitaxel followed by pegfilgrastim on day 2. On day 3, her white blood cell count was 123,310/mm³. Patients 2 and 3 experienced fever and neutropenia several weeks after the last dose of chemotherapy and pegfilgrastim. Both Burstein et al.¹⁴ and Wolff et al.¹⁵ reported patients in whom pegfilgrastim was held for leukocytosis during the paclitaxel cycles, and who subsequently developed grade 3 or 4 neutropenia. They caution against withholding MGF support. Wolff et al.¹⁵ suggest substituting a short course of filgrastim for pegfilgrastim in patients who have a high day-1 ANC as a possible approach.

Brusalamino et al.¹⁶ reported the successful use of pegfilgrastim for hematopoietic support given on day 3 for patients treated with dose-dense R-CHOP-14, allowing on-time delivery of chemotherapy in 92% of cycles and a low incidence of febrile neutropenia (4% of cycles). NCCN guidelines state that phase II studies show efficacy in chemotherapy regimens given every 2 weeks.¹

Same-Day Filgrastim Schedule: Based on the potential that exposing neutrophils stimulated by a MGF to chemotherapy may produce increased neutropenia, same-day administration of chemotherapy and MGFs

should be avoided.² Some trials have reported increased myelotoxicity with same-day filgrastim and chemotherapy, notably with fluorouracil and with topotecan.^{17,18} Studies also have reported an apparent increase in nonhematologic toxicity with same-day filgrastim administration.¹⁹ Other studies have reported that same-day filgrastim has been well tolerated.²⁰⁻²² The variability in findings may be a function of the mechanism of action and schedule of chemotherapy. Because little benefit is gained in convenience from same-day filgrastim administration, and various reports of potential for increased hematologic and nonhematologic toxicity, the use of same-day filgrastim should be used only within the context of a clinical trial.¹⁹

Same-day Pegfilgrastim:

Trials Supporting Same-Day Pegfilgrastim: Vance and Carpenter²³ reported a retrospective review of same-day pegfilgrastim in 64 patients with breast cancer treated with dose-dense doxorubicin and found no granulocytopenia or febrile neutropenia, and therefore concluded that same-day pegfilgrastim with doxorubicin is safe and effective.

Lokich²⁴ describes the use of same-day pegfilgrastim given every 2 weeks in 80 patients treated with weekly chemotherapy, and concludes pegfilgrastim can be safely administered every 2 weeks to maintain a weekly chemotherapy schedule.

Hoffmann²⁵ performed a retrospective review of patient records to compare the safety of same-day with next-day pegfilgrastim. The data were collected from a community-based oncology practice, and included 159 treatments for 15 tumor types and 50 chemotherapy regimens. The review found similar incidence of myelosuppressive adverse events between the groups.

Belani et al.²⁶ reported the results of a randomized double-blind phase II study of same-day versus next-day pegfilgrastim in patients with non-small cell lung cancer treated with carboplatin and docetaxel. The study found similar incidence of grade 3 or 4 neutropenia among the groups. No patients developed febrile neutropenia.

Trials Against Using Same-day Pegfilgrastim: Kaufman et al.²⁷ reported the results of a phase II study evaluating same-day versus next-day administration of pegfilgrastim with docetaxel, doxorubicin, and cyclophosphamide (TAC) in women with early-stage and advanced breast cancer. They found a significant difference in rates of febrile neutropenia between the groups. The incidence

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of febrile neutropenia was 33% in the same-day group compared with 11% in the next-day group.

Martin et al.²⁸ describe a 24% incidence of febrile neutropenia in patients treated with TAC who receive no MGF support. Yardley et al.²⁹ describe same-day pegfilgrastim in dose-dense adjuvant therapy for breast cancer using docetaxel followed by doxorubicin/cyclophosphamide. They reported a higher-than-expected incidence of grade 3 and 4 arthralgias during docetaxel therapy, which may be caused by pegfilgrastim. Myelotoxicity from docetaxel was low, and was possibly decreased by pegfilgrastim. During the cycles of doxorubicin and cyclophosphamide, a higher-than-expected incidence of grade 3 and 4 neutropenia, and febrile neutropenia was observed, to which same-day pegfilgrastim may have contributed.

Saven et al.³⁰ describe a prospective randomized double-blind trial of same-day versus next-day pegfilgrastim in patients undergoing R-CHOP chemotherapy for lymphoma, reporting a longer duration of grade 4 neutropenia in the same-day group but with no difference in incidence of febrile neutropenia or dose intensity. Lokich³¹ reports a similar finding in a retrospective review of 10 patients who underwent CHOP or CHOP-like therapy for NHL with pegfilgrastim given on a same-day schedule. He found no abrogation of leukopenia compared to patients who received no pegfilgrastim, and found what appeared to be enhanced myelosuppression in patients treated with same-day pegfilgrastim.

Pegfilgrastim should be administered no sooner than 24 hours after cytotoxic chemotherapy is administered. This is consistent with the FDA-approved prescribing information, and NCCN and ASCO guidelines. If the patient cannot be treated with next-day pegfilgrastim for logistical reasons, same-day pegfilgrastim should be considered only for those regimens in which same-day pegfilgrastim has shown acceptable efficacy. In particular, CHOP regimens for lymphoma and doxorubicin/cyclophosphamide regimens for breast cancer seem to be therapy in which same-day pegfilgrastim should be avoided.

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