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Spotlight on Pegfilgrastim in Chemotherapy-Induced Neutropenia[1]

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Contents

Abstract

Pegfilgrastim (Neulasta®), the sustained-duration form of filgrastim (recombinant human granulocyte colony-stimulating factor [G-CSF]), is created by the addition of a polyethylene glycol (PEG) moiety to filgrastim. Its approved indication in the US is to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive chemotherapy.

A single subcutaneous injection of pegfilgrastim once per chemotherapy cycle was more effective than placebo as an adjunct to moderately myelosuppressive chemotherapy for breast cancer, no less effective than daily injections of filgrastim as an adjunct to highly myelosuppressive chemotherapy for breast cancer, and as effective as daily filgrastim as an adjunct to chemotherapy for lymphoma (predominantly non-Hodgkin lymphoma [NHL]) and acute myeloid leukemia. Pegfilgrastim has also successfully supported delivery of dose-dense chemotherapy, stem cell mobilization, and stem cell transplantation after high-dose chemotherapy in patients with non-myeloid or myeloid malignancies. By offering a convenient alternative to daily filgrastim, once-per-cycle administration of pegfilgrastim has the potential to simplify the management of chemotherapy-induced neutropenia, further improve patient health-related quality of life, and reduce total treatment costs in breast cancer and NHL, and possibly other cancer settings. Pegfilgrastim should, likewise, permit simplification of G-CSF–based stem cell mobilization and transplantation procedures.

1. Pharmacological Properties

Pegfilgrastim is produced by covalently binding a 20 kDa polyethylene glycol (PEG) molecule to the *N*-terminal methionyl residue of filgrastim.[1] Pegfilgrastim and filgrastim share the same mechanism of action (stimulation of granulocytopoiesis) and pharmacodynamic profile (e.g. elevation of absolute neutrophil count [ANC] and reduction in duration of chemotherapy-induced neutropenia);[2] both recombinant human granulocyte colony-stimulating factors (G-CSFs) are administered by the subcutaneous route. However, the greater weight and size of the pegfilgrastim molecule results in reduced renal clearance, an increased terminal elimination half-life, and hence a sustained duration of action relative to filgrastim.[3,4] In patients with chemotherapy-induced neutropenia after myelosuppressive chemotherapy, plasma concentrations of pegfilgrastim remained elevated throughout the ANC nadir and declined rapidly as ANC recovered.[4-6] This is consistent with the suggestion that self-regulating, neutrophil-mediated clearance, rather than renal elimination, is the predominant route of elimination of pegfilgrastim.[7]

1 This spotlight is derived from abstract and summary text of an Adis Drug Evaluation originally published in full in *American Journal of Cancer* 2005; 4 (4): 255-74. Reviewers of the original full text article are listed in the Acknowledgments section.

2. Therapeutic Efficacy

The efficacy of subcutaneous pegfilgrastim once per cycle in providing neutrophil support after standard regimens of myelosuppressive chemotherapy has been demonstrated in patients, most of whom were previously untreated, with breast cancer[6,8,9] or lymphomas (non-Hodgkin lymphoma [NHL] or Hodgkin disease),[10-12] or acute myeloid leukemia (AML).[13]

In large, noninferiority, pivotal, phase III trials in patients with high-risk stage II–IV breast cancer[6,9] and a phase II trial in patients with lymphoma (predominantly NHL),[10] a fixed (6mg) or bodyweight-based (100 μg/kg) dose of pegfilgrastim administered once per chemotherapy cycle was no less effective than daily filgrastim 5 μg/kg (mean/median ≈11 doses per cycle) in reducing chemotherapy-induced neutropenia after highly myelosuppressive chemotherapy. In the studies in patients with breast cancer,[6,9] which were identical except for the mode of pegfilgrastim dosing, between-group differences in the mean duration of severe neutropenia (ANC $<0.5 \times 10^9$/L) during the first chemotherapy cycle (primary endpoint) were <1 day, thus satisfying the noninferiority criteria for pegfilgrastim versus filgrastim. A similar outcome was seen in the NHL trial,[10] although this was not formally designed as a noninferiority study.

Notwithstanding the noninferiority design of the studies in patients with breast cancer,[6,9] a significant reduction in the incidence of febrile neutropenia across all chemotherapy cycles was seen with pegfilgrastim versus filgrastim in the trial of pegfilgrastim 100 μg/kg per cycle (9% vs 18%)[9] as well as in a combined analysis of both trials (11% vs 19%).[14] Additionally, subset analyses in the studies in patients with breast cancer suggested that the effect of pegfilgrastim on the duration of severe neutropenia following one or all (four) cycles of chemotherapy was similar regardless of prior chemotherapy or radiotherapy exposure and, in patients receiving pegfilgrastim 6mg per cycle, irrespective of bodyweight.[6,9]

Relative to placebo, pegfilgrastim 6mg once per cycle significantly reduced rates of febrile neutropenia (17% vs 1%), hospitalization (14% vs 1%) and intravenous anti-infectives (10% vs 2%) over all cycles in a large, randomized, double-blind, phase III trial in 928 patients with stage I–IV breast cancer who received moderately myelosuppressive chemotherapy.[8]

Pegfilgrastim was also effective in supporting the delivery of dose-dense cytotoxic chemotherapy regimens for previously untreated solid tumors (breast cancer[15,16] and small cell lung cancer[17]) and lymphomas (NHL[18,19] and Hodgkin disease[20,21]).

Pegfilgrastim, alone or in combination with myelosuppressive chemotherapy, successfully mobilized CD34+ cells in patients with solid tumors, lymphomas, or multiple myeloma;[4,22-24] it also supported stem cell transplantation after high-dose chemotherapy in patients with lymphomas or multiple myeloma.[25]

Pegfilgrastim was, in general, at least as effective as daily filgrastim based on 'head-to-head' and/or retrospective comparisons conducted in the settings of AML,[13] dose-dense chemotherapy,[18] and stem cell mobilization.[23]

3. Tolerability

Pegfilgrastim was generally well tolerated in a total of 465 patients with solid tumors or lymphomas undergoing myelosuppressive chemotherapy in clinical trials; the drug had an adverse event profile (including changes in laboratory values) similar to that of filgrastim.[26]

Medullary bone pain was the most common treatment-related adverse event with pegfilgrastim, occuring in approximately one-quarter of patients who received the drug in clinical trials.[26] The incidence, severity, and duration of bone pain with a single injection of pegfilgrastim 6mg or 100 μg/kg per cycle was not significantly different from that with daily doses of filgrastim 5 μg/kg in the two pivotal phase III trials in patients with breast cancer.[6,9,27] However, if bone pain occurred, the onset was earlier after the initial and final cycles of chemotherapy in the fixed-dose trial of pegfilgrastim 6mg once per cycle.[6,27] Bone pain was generally of mild-to-moderate intensity and usually resolved with non-narcotic analgesics.[27]

In the large, noninferiority, phase III studies in patients with breast cancer,[6,9] transient elevations in plasma levels of lactate dehydrogenase, alkaline phosphatase, and uric acid with pegfilgrastim were not clinically significant, and no neutralizing antibodies against the drug were detected.

4. Pharmacoeconomic Considerations

Preliminary reports of economic modelling studies based on outcomes in the two pivotal phase III trials in patients with breast cancer suggested that once-per-cycle pegfilgrastim 6mg or 100 μg/kg may reduce total chemotherapy-induced neutropenia management costs over all four cycles relative to daily filgrastim 5 μg/kg.[28-30]

According to other preliminary reports, universal (i.e. non-targeted) primary prophylaxis with pegfilgrastim is predicted to be cost saving compared with no G-CSF treatment when the risk of developing febrile neutropenia in the first chemotherapy cycle is >23% in patients receiving cyclophosphamide, doxorubicin, vincristine, and prednisolone for NHL and >16% in patients receiving docetaxel, with or without doxorubicin, for breast cancer.[31,32]

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