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Pegfilgrastim

Monique P. Curran and *Karen L. Goa*

Adis International Limited, Auckland, New Zealand

Contents

Abstract

▲ Pegfilgrastim is a covalent conjugant of filgrastim (a recombinant human granulocyte colony-stimulating factor) and monomethoxypolyethylene glycol. It is administered as a single dose per myelosuppressive chemotherapy cycle to decrease the incidence of infection, as manifest by febrile neutropenia, in patients with nonmyeloid cancer.

▲ Pegfilgrastim increases the terminal elimination half-life and decreases the apparent serum clearance of the drug in patients with nonmyeloid cancer. Serum concentrations of pegfilgrastim remain elevated during neutropenia but decline when the neutrophil count increases.

▲ In phase III trials in patients with breast cancer and in a phase II trial in patients with non-Hodgkin's lymphoma or Hodgkin's disease, the mean duration of grade 4 neutropenia and the time to absolute neutrophil recovery during cycle 1 of chemotherapy was similar in recipients of single-dose pegfilgrastim or daily filgrastim.

▲ In the larger of two phase III trials in patients with breast cancer, the incidence of febrile neutropenia over four cycles of chemotherapy was significantly lower in recipients of single-dose pegfilgrastim than that in recipients of daily injections of filgrastim. Moreover, the mean duration of grade 4 neutropenia in cycles 2 to 4 of chemotherapy was significantly lower in recipients of pegfilgrastim than that in recipients of daily filgrastim.

▲ In comparative trials, there were no differences in the incidence and severity of adverse events, including skeletal pain, between single-dose pegfilgrastim and daily filgrastim in patients with nonmyeloid cancer receiving myelosuppressive chemotherapy.

Features and properties of pegfilgrastim	
Indication	
To decrease the incidence of infection, as manifest by febrile neutropenia, in patients with nonmyeloid malignancies who are receiving myelosuppressive anticancer agents	
Mechanism of action	
Recombinant human granulocyte colony-stimulating factor (pegylated)	Stimulates the activation, proliferation and differentiation of progenitor cells and enhances the functions of mature neutrophils
Dosage and administration	
Recommended dose	6mg (protein weight)
Route of administration	Subcutaneous
Frequency of administration	Single dose administered once per chemotherapy cycle
Pharmacokinetic profile (single dose of subcutaneous pegfilgrastim 100 μg/kg administered 24h after chemotherapy; median values; n = 3)	
Peak plasma concentration	114 μg/L
Time to peak plasma concentration	72h
Area under the plasma concentration-time curve	7150 μg/h • L
Terminal elimination half-life	33.2h
Apparent serum clearance	14 ml/h/kg
Adverse events	
Not significantly different from filgrastim	
Most frequent drug-related	Skeletal pain

1. Introduction

Neutropenia is a serious and frequent complication in patients receiving myelosuppressive anticancer drugs. It is associated with an increased risk of infections which may be life-threatening and require hospitalisation or intravenously administered antibiotics.[1,2] Many of the signs and symptoms of infection may be absent or muted in patients with neutropenia; however, fever usually develops.[1] Although definitions vary, generally patients with a single temperature >38.0°C associated with an absolute neutrophil count (ANC) of $<0.5 \times 10^9$/L have been defined as having febrile neutropenia.[1]

Filgrastim, a recombinant human granulocyte colony-stimulating factor (G-CSF) derived from *Escherichia coli*, is effective in the prevention of chemotherapy-induced neutropenic complications in patients with cancer. The pharmacological properties, efficacy, tolerability and pharmacoeconomic properties of filgrastim in patients with neutropenia have previously been reviewed in *Drugs*.[3,4] Filgrastim has identical biological activity to that of endogenous human G-CSF. It stimulates the activation, proliferation and differentiation of neutrophil progenitor cells and enhances the functions of mature neutrophils. However, filgrastim has a short elimination half-life and requires daily subcutaneous injections for up to 2 weeks of each chemotherapy cycle for the prevention of neutropenic complications in patients with nonmyeloid cancer.[4]

By increasing the apparent molecular size, pegylation can significantly decrease the clearance of a protein from the plasma, thus increasing its half-life.[5] Moreover, this approach allows such pegylated proteins to be administered less frequently than the unpegylated formulation.[2]

Pegfilgrastim has been formed by the covalent attachment of a 20 kilodalton monomethoxy polyethylene glycol molecule to the N-terminal methionyl residue of filgrastim. The pharmacological properties of the pegylated formulation of filgrastim are outlined in this profile. The profile also focuses on the efficacy and tolerability of this formulation, administered as a single dose per cycle of myelosuppressive chemotherapy, in the prevention of neutropenic complications in patients with nonmyeloid malignancies.

2. Pharmacodynamic Profile

The pharmacodynamic properties of pegfilgrastim are similar to those of filgrastim (reviewed in *Drugs*[4]). This haematopoietic growth factor acts primarily to stimulate proliferation and differentiation of committed progenitor cells of the granulocyte-neutrophil lineage into functionally mature neutrophils. The pharmacodynamic properties of pegfilgrastim are briefly outlined below and are compared with those of filgrastim in animal[6-9] and clinical studies.[6,10,11]

Animal Studies

- Pegfilgrastim was as effective as filgrastim in increasing and sustaining neutrophil counts in normal and neutropenic mice[6,7] and in primate models of myelosuppression[8] (study reported as an abstract). In normal mice, a single subcutaneous injection of pegfilgrastim 1 mg/kg resulted in a maximum neutrophil count (15.5×10^9/L) similar to that achieved with subcutaneous injections of filgrastim 125 μg/kg twice daily for 4 days (25.7×10^9/L).[7] Similarly in neutropenic mice, the maximum neutrophil counts were 24.0 and 18.0×10^9/L, respectively.[7] In normal mice injected with a single dose of pegfilgrastim, neutrophil counts remained elevated for 5 days.[6] In myelosuppressed rhesus monkeys,[8] the duration of neutropenia (ANC $<0.5 \times 10^9$/L) was similar in animals treated with a single subcutaneous injection of pegfilgrastim 300 μg/kg (13.7 days) and in animals treated with daily injections (for up to 21 days) of filgrastim 10 μg/kg/day (9.5 days).[8]
- Pegfilgrastim was effective in stimulating the mobilisation of peripheral blood progenitor cells (PBPC) in mice.[6,9] Granulocyte macrophage colony-forming cells were used as markers of PBPC. Daily injections of filgrastim 200 μg/kg/day resulted in a 100-fold increase from baseline in PBPC in the blood over the 5-day treatment period.[6] In contrast, a single injection of

pegfilgrastim 1000 μg/kg resulted in a 3-fold higher relocation of PBPC than that attained with daily filgrastim.[6] Moreover, the peak in PBPC numbers occurred earlier with pegfilgrastim (day 3) than with daily filgrastim (day 4 to 5).

Clinical Studies

Effects on Neutrophils

• In healthy volunteers[6] and in patients with cancer not treated with chemotherapy,[10] administration of a single subcutaneous injection of pegfilgrastim 30 to 300 μg/kg resulted in a dose-dependent increase in ANC from baseline. Moreover, the maximum ANC (ANC_{max}) obtained and the duration of the increase were also dose-dependent.[6,10] For example, in a randomised study in 13 patients with non-small cell lung cancer (NSCLC), the median ANC_{max} for a single injection of pegfilgrastim 30, 100 or 300 μg/kg was 24, 32 and 54×10^9/L, respectively.[10]

• The ANC_{max} with a single injection of pegfilgrastim 100 μg/kg was similar to that with daily filgrastim 5 μg/kg/day administered for 5 days in 13 patients with NSCLC not treated with chemotherapy.[10] However, the duration of the increase in ANC was more sustained in recipients of single-dose pegfilgrastim 30 to 300 μg/kg than that in recipients of daily filgrastim 5 μg/kg/day (data presented graphically; statistical analysis not reported).

• In chemotherapy-treated patients with cancer,[10,12] the ANC profiles obtained after treatment with single-dose pegfilgrastim 100 μg/kg or daily filgrastim 5 μg/kg/day were similar. Both treatment groups showing an initial slight increase in ANC followed by the chemotherapy-induced ANC nadir and then a postnadir ANC recovery.

• In 13 patients with cancer who had received chemotherapy, treatment with single-dose pegfilgrastim 100 and 300 μg/kg resulted in a higher median ANC nadir (0.65 and 0.7×10^9/L, respectively) than single-dose pegfilgrastim 30 μg/kg and daily filgrastim 5 μg/kg/day (both 0.1×10^9/L; p values not stated).[10] Median ANC was $>10 \times 10^9$/L within 10 days of administration of single-dose pegfilgrastim 100 and 300 μg/kg.[10]

• Neutrophil respiratory burst activities (as measured by oxidase-dependent and myeloperoxidase-dependent luminescence) were stimulated to a similar extent in volunteers who received daily subcutaneous injections of filgrastim 5 μg/kg/day for 10 days (n = 8) and single subcutaneous injections of pegfilgrastim 30 μg/kg (n = 8) or 60 μg/kg (n = 8); this study was presented as an abstract.[11]

Effects on Other Cell Types

• Administration of single-dose pegfilgrastim 30 to 300 μg/kg resulted in mobilisation of $CD34^+$ cells in volunteers[6] and in patients with cancer before and after chemotherapy.[10] In patients with NSCLC, the median peak $CD34^+$ cell count in recipients of pegfilgrastim 30, 100 and 300 μg/kg was 12.3, 60.5 and 42.7 cells/μL, respectively, prior to chemotherapy and 4.8, 67.8 and 27.9 cells/μL, respectively, after chemotherapy. The median peak $CD34^+$ cell count in recipients of daily filgrastim 5 μg/kg/day before and after chemotherapy was 14.6 and 56.8 cells/μL, respectively.[10] Significant interpatient variability in $CD34^+$ cell mobilisation was reported.[10]

3. Pharmacokinetic Profile

The pharmacokinetic properties of single-dose pegfilgrastim were assessed in 10 patients with NSCLC[10,13] and in 129 patients with breast cancer.[13] Studies were reported in full[10] or as an abstract.[13] Patients with NSCLC were treated with one cycle of carboplatin/paclitaxel[10,13] and patients with breast cancer were treated with one cycle of doxorubicin/docetaxel.[13] Pegfilgrastim was administered subcutaneously over a range of 30 to 300 μg/kg in patients with NSCLC[10,13] and 30 to 100 μg/kg in patients with breast cancer.[13] In patients with cancer, a single dose of subcutaneous pegfilgrastim was administered before[10,13] or 24 hours after chemotherapy.[10,13]

• Peak serum concentrations (C_{max}) and area under the concentration-time curve (AUC) increased with increasing dose of pegfilgrastim in patients

with cancer before and after chemotherapy.[10,13] These increases were nonlinear over the ranges evaluated. For example, after administration of single-dose pegfilgrastim 30, 100 and 300 μg/kg to chemotherapy-treated patients with NSCLC, median C_{max} values were 7.15, 114 and 945 μg/L and median $AUC_{0-\infty}$ values were 741, 7150 and 137 000 μg/h • L, respectively.[10]

• Pegylation of filgrastim increases the elimination half-life ($t_{1/2}$) in patients with cancer before and after chemotherapy.[10] In chemotherapy-treated patients with NSCLC, the median $t_{1/2}$ values of single-dose pegfilgrastim 100 μg/kg and single-dose filgrastim 5 μg/kg were 33.2 and 3.37 hours, respectively, an approximately 10-fold increase.[10]

• Pegylation of filgrastim also increased the time to reach maximum plasma concentration (t_{max}) in patients with cancer before and after chemotherapy.[10] After administration of single-dose pegfilgrastim 100 μg/kg and a single dose of filgrastim 5 μg/kg, median t_{max} values were 72 and 8 hours, respectively, in chemotherapy-treated patients with NSCLC.[10]

• The serum clearance of pegfilgrastim decreased with increasing dose of pegfilgrastim in patients with cancer before and after chemotherapy.[10,13] The median apparent serum clearance of single-dose pegfilgrastim 30, 100 and 300 μg/kg in chemotherapy-treated patients with NSCLC was 40.5, 14.0 and 2.19 ml/h/kg, respectively.[10] The median serum clearance of single-dose pegfilgrastim 30 and 100 μg/kg in chemotherapy-treated patients with breast cancer was 26.4 and 6.7 ml/h/kg, respectively.[13]

• The median apparent serum clearance with single-dose pegfilgrastim 100 μg/kg was lower than that with a single dose of filgrastim 5 μg/kg (14.0 *vs* 39.6 ml/h/kg, respectively) in chemotherapy-treated patients with NSCLC.[10]

• In chemotherapy-treated patients with cancer,[10,13] serum concentrations of pegfilgrastim remained elevated during neutropenia but declined when the neutrophil count started to increase, suggesting that pegfilgrastim elimination is dependent on neutrophil-mediated elimination. A cytokinetic model based on data from 32 healthy volunteers who received single-dose pegfilgrastim 30 to 300 μg/kg also predicted the neutrophil-dependent regulation of the drug.[14]

4. Therapeutic Trials

Two randomised, multicentre, double-blind phase III trials have investigated the efficacy of single-dose pegfilgrastim administered once per cycle of chemotherapy in the prevention of chemotherapy-induced neutropenia in patients with stage II to IV breast cancer; one study was published in full[12] and the other study was reported as an abstract.[15] Patients (n = 310[12] or 157[15]) received four 21-day cycles of chemotherapy (doxorubicin 60 mg/m^2 and docetaxel 75 mg/m^2). They were randomised to receive a single subcutaneous injection of pegfilgrastim 100 μg/kg[12] or 6mg[15] or daily subcutaneous injections of filgrastim 5 μg/kg/day.

The efficacy of single-dose pegfilgrastim was also investigated in a randomised, nonblind, phase II trial (presented as an abstract) in patients with refractory non-Hodgkin's lymphoma or Hodgkin's disease (n = 60) treated with chemotherapy (etoposide, methylprednisolone, cisplatin and cytarabine).[16] Patients were randomised to receive a single subcutaneous injection of pegfilgrastim 100 μg/kg or daily subcutaneous injections of filgrastim 5 μg/kg/day.

Daily filgrastim was administered until either a post-nadir ANC ≥10 x 10^9/L[12,15,16] or for up to 12[16] or 14[12,15] days. Filgrastim was administered for a mean of 11 daily injections in two of the trials.[12,16] Administration of the filgrastim and the pegylated formulation was initiated approximately 24 hours after the completion of chemotherapy.[12,15,16] Single-dose pegfilgrastim recipients continued with placebo injections for up to 2 weeks to maintain blinding.[12,15]

The primary end-point in all studies[12,15,16] was the duration of grade 4 neutropenia (ANC <0.5 × 10^9/L) in cycle 1 of chemotherapy. In one phase III study, per-protocol results were reported for 130

evaluable patients with breast cancer.[15] In the other phase III study, 147 patients treated with single-dose pegfilgrastim and 149 patients treated with daily filgrastim were evaluated for intent-to-treat analysis.[12]

• In the two randomised, multicentre trials in patients with breast cancer, the mean duration of grade 4 neutropenia during cycle 1 of chemotherapy was similar in recipients of a single injection of pegfilgrastim to that in recipients of daily injections of filgrastim (figure 1).[12,15] Similarly, in patients with non-Hodgkin's lymphoma or Hodgkin's disease, the mean duration of grade 4 neutropenia during cycle 1 was similar in recipients of single-dose pegfilgrastim and daily filgrastim (2.8 and 2.4 days, respectively).[16]

• In cycles 2 to 4 of chemotherapy, the mean duration of grade 4 neutropenia in recipients of a single injection of pegfilgrastim 100 μg/kg (0.6 to 0.9 days) was significantly lower than that in recipients of daily filgrastim 5 mg/kg/day (1.1 to 1.3 days) in the larger phase III study in patients with breast cancer ($p \leq 0.02$ for each comparison).[12]

• The incidence of febrile neutropenia (oral temperature ≥38.2°C and ANC <0.5 x 10^9/L) over the four cycles of chemotherapy was lower in recipients of a single injection of pegfilgrastim administered once per chemotherapy cycle than that in recipients of daily injections of filgrastim administered for up to 14 days per chemotherapy cycle in both phase III trials in patients with breast cancer; this difference was significant in the larger study[12] (figure 2). [12,15] In the study in patients with non-Hodgkin's lymphoma or Hodgkin's disease, the cumulative incidence of febrile neutropenia in cycles 1 and 2 was similar in recipients of single-dose pegfilgrastim and daily filgrastim (21 *vs* 19%).[16]

• The time to ANC recovery (time from chemotherapy until the patient's ANC increased to 2.0 × 10^9/L after the expected nadir) in cycle 1 was similar in recipients of single-dose pegfilgrastim and daily filgrastim in patients with breast cancer (mean 9.3 *vs* 9.7 days)[12] and in patients with non-Hodgkin's lymphoma or Hodgkin's disease (median 16 *vs* 15 days).[16]

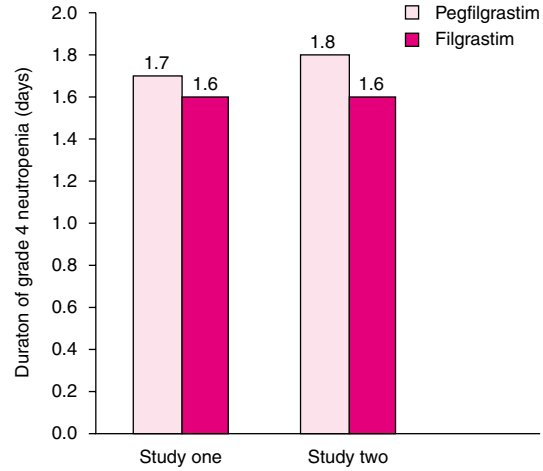

Fig. 1. Duration of grade 4 neutropenia during cycle 1 of chemotherapy (doxorubicin 60 mg/m^2 and docetaxel 75 mg/m^2) in patients with stage II to IV breast cancer in two multicentre, randomised, double-blind, phase III trials.[12,15,17] In study one, 310 patients were randomised to received a single subcutaneous injection of pegfilgrastim 100 μg/kg per 21-day chemotherapy cycle or daily subcutaneous injections of filgrastim 5 μg/kg/day.[12] In study two, 157 patients were randomised to received a single subcutaneous injection of pegfilgrastim 6mg per chemotherapy cycle or daily subcutaneous injections of filgrastim 5 μg/kg/day.[15,17] Data presented in the figure have been obtained from the package insert.[17] In both studies, patients received daily filgrastim until either a post-nadir ANC ≥10 x 10^9/L or for up to 14 days.

• In one phase III trial in patients with breast cancer,[12] patients treated with a single injection of pegfilgrastim tended to have higher nadir ANC than patients treated with daily injections of subcutaneous filgrastim over the four cycles of chemotherapy.

5. Tolerability

• In the two phase III trials in patients with breast cancer (total of 431 evaluable patients)[12,15] and the phase II trial in 60 patients with non-Hodgkin's lymphoma or Hodgkin's disease[16] discussed earlier (see section 4 for details), the incidence and severity of adverse events was similar in recipients of a subcutaneous injection of pegfilgrastim (100 μg/kg[12,16] or 6mg[15] administered once per che-

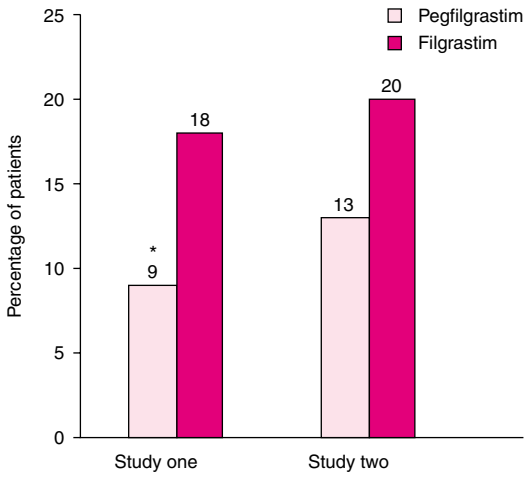

Fig. 2. Incidence of febrile neutropenia (≥38.2°C oral temperature and an absolute neutrophil count <0.5 x 10^9/L) over all four cycles of chemotherapy (doxorubicin 60 mg/m^2 and docetaxel 75 mg/m^2) in patients with stage II to IV breast cancer in two multicentre, randomised, double-blind, phase III trials.[12,15] In study one, patients were randomised to received a single subcutaneous injection of pegfilgrastim 100 μg/kg per 21-day chemotherapy cycle (n = 147) or daily subcutaneous injections of filgrastim 5 μg/kg/day (n = 149).[12] In study two, patients received a single subcutaneous injection of pegfilgrastim 6mg per chemotherapy cycle (n = 68) or daily subcutaneous injections of filgrastim 5 μg/kg/day (n = 62).[15] In both studies, patients received daily filgrastim until either a post-nadir ANC ≥10 x 10^9/L or for up to 14 days. Intent-to-treat[12] or per-protocol results[15] were reported. * p = 0.029 *vs* filgrastim.

motherapy cycle) and daily subcutaneous injections of filgrastim 5 μg/kg/day administered for up to 2 weeks per chemotherapy cycle. Most adverse events were attributed by the researchers to cytotoxic chemotherapy or the underlying malignancy.[12]

• The incidence of skeletal pain was similar in recipients of single-dose pegfilgrastim and daily filgrastim in phase III trials in patients with breast cancer,[12,15] and in a phase II trial in patients with non-Hodgkin's lymphoma or Hodgkin's disease.[16] Skeletal pain was the most commonly reported adverse event in one of the phase III trials,[12] occurring in 25% of 150 evaluable patients treated with single-dose pegfilgrastim 100 μg/kg and 26% of 151 evaluable patients treated with daily filgrastim 5 μg/kg/day. No patients withdrew from the clinical trials because of bone pain.[17]

• In the same trial,[12] the incidence of withdrawals related to adverse events was similar in patients treated with single-dose pegfilgrastim (4%) and those patients treated with daily filgrastim (3%).

•The incidence anaemia of at least grade 3 was also similar in recipients of single-dose pegfilgrastim and daily filgrastim (7 *vs* 10%).[12] Grade 4 thrombocytopenia was reported in <5% of patients over all cycles of chemotherapy treatment. No neutralising antibodies were detected during the study.

6. Dosage and Administration

In the US, pegfilgrastim is indicated to decrease the incidence of infection, as manifest by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia.[17] The recommended dosage of pegfilgrastim is a single subcutaneous injection of 6mg dose (based on protein weight) administered once per chemotherapy cycle.[17] Pegfilgrastim should not be administered in the period between 14 days before and 24 hours after administration of cytotoxic chemotherapy. Pegfilgrastim should not be used in infants or smaller adolescents weighing <45kg. It is contraindicated in patients with known hypersensitivity to *E. coli*-derived proteins, pegfilgrastim, filgrastim or any other component of the product. Rare cases of splenic rupture have been reported in patients treated with filgrastim for PBPC mobilisation; since the tolerability and efficacy of pegfilgrastim in this setting have not be been evaluated, pegfilgrastim should not be used for PBPC mobilisation. Pegfilgrastim should be discontinued in patients who develop adult respiratory distress syndrome and should be used with caution in patients with sickle cell disease. Allergic reactions have been reported in recipients of filgrastim; however, allergic reactions to the pegylated formulation have not been reported in clinical trials.[17]

7. Current Status

Pegfilgrastim, administered as a single subcutaneous 6mg dose per chemotherapy cycle, has been approved by the US Food and Drug Administration to reduce the incidence of infection, as manifest by febrile neutropenia, in patients with nonmyeloid malignancies who are receiving myelosuppressive anticancer drugs that are associated with a clinically significant incidence of febrile neutropenia. In two phase III trials in patients with breast cancer, pegfilgrastim (one single dose per chemotherapy cycle) provided similar efficacy and tolerability as filgrastim (administered daily for up to 2 weeks per chemotherapy cycle).

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Correspondence: *Monique P. Curran*, Adis International Limited, Auckland, New Zealand.
E-mail: demail@adis.co.nz