Original article

Annals of Oncology 14: 29–35, 2003
DOI: 10.1093/annonc/mdg019

A randomized double-blind multicenter phase III study of fixed-dose single-administration pegfilgrastim versus daily filgrastim in patients receiving myelosuppressive chemotherapy

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Received 20 March 2002; revised 3 June 2002; accepted 17 July 2002

Background: We evaluated the efficacy of a single fixed 6 mg dose of pegfilgrastim (a pegylated version of filgrastim) per cycle of chemotherapy, compared with daily administration of filgrastim, in the provision of neutrophil support.

Patients and methods: Patients (n = 157) were randomized to receive either a single 6 mg subcutaneous (s.c.) injection of pegfilgrastim or daily 5 mg/kg s.c. injections of filgrastim, after doxorubicin and docetaxel chemotherapy (60 mg/m^2 and 75 mg/m^2, respectively). Duration of grade 4 neutropenia, depth of neutrophil nadir, incidence of febrile neutropenia, time to neutrophil recovery and safety information were recorded.

Results: A single 6 mg injection of pegfilgrastim was as effective as daily injections of filgrastim for all efficacy measures for all cycles. The mean duration of grade 4 neutropenia in cycle 1 was 1.8 and 1.6 days for the pegfilgrastim and filgrastim groups, respectively. Results for all efficacy end points in cycles 2–4 were consistent with the results from cycle 1. A trend towards a lower incidence of febrile neutropenia was noted across all cycles with pegfilgrastim compared with filgrastim (13% versus 20%, respectively). A single fixed dose of pegfilgrastim was as safe and well tolerated as standard daily filgrastim.

Conclusions: A single fixed dose of pegfilgrastim administered once per cycle of chemotherapy was comparable to multiple daily injections of filgrastim in safely providing neutrophil support during myelosuppressive chemotherapy. Pegfilgrastim may have utility in other clinical settings of neutropenia.

Key words: breast cancer, clinical trial, hemopoietic growth factor, multicenter study, neutropenia

Introduction

Myelosuppression is the primary toxicity of many chemotherapy regimens and limits their applicability. Furthermore, both the duration of grade 4 neutropenia and the depth of the neutrophil nadir after chemotherapy are correlated with the development of infectious complications [1–6]. As a result, the prevention of neutropenia is a relevant goal of daily oncological practice, for both patient safety and cost-efficiency.

Filgrastim (r-metHuG-CSF) stimulates the production of neutrophil precursors, enhances the function of mature neutrophils, and ameliorates neutropenia and its complications (for a review see [7]). Filgrastim is cleared by renal- [8] and neutrophil-mediated [9] mechanisms, has a plasma half-life of 3–4 h [3] and requires daily administration [10]. Proteins can be modified to significantly increase their half-life by the chemical addition of polyethylene glycol (PEG) [11]. PEG-modification of filgrastim results in a new molecule called pegfilgrastim, which in both experimental animals and healthy human volunteers has decreased renal clearance and increased plasma half-life compared with filgrastim, thus sustaining the duration of the pharmacological effect [8]. Median plasma half-life values of pegfilgrastim are independent of dose, and range from 46 to 62 h (unpublished data; Amgen Inc. Thousand Oaks, CA, USA). Results of preclinical studies suggest that the biological activity of pegfilgrastim and filgrastim are similar, but with pegfilgrastim only requiring a single injection per chemotherapy cycle to achieve the same effect as multiple daily injections of filgrastim [8]. The sustained-duration effect of pegfilgrastim is attributable to reduced renal clearance compared with filgrastim; its clearance is regulated

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predominantly by neutrophils and their precursors [12]. Potential benefits of pegfilgrastim over daily administration of other G-CSF (granulocyte colony-stimulating factor) products include fewer injections (i.e. once per chemotherapy cycle), leading to a greater likelihood of patient compliance (with respect to missed doses), and decreased burden for both patients and healthcare professionals.

The aim of this study was to evaluate the efficacy of a single fixed 6 mg dose of pegfilgrastim per cycle of chemotherapy, compared with daily administration of filgrastim, in the provision of neutrophil support for patients receiving myelosuppressive chemotherapy.

Patients and methods

Study population

The institutional review boards or ethics committees of the participating centers approved the protocol. Written informed consent was obtained from all patients before any study-related procedure was performed.

Thirty-seven centers in Europe, Australia and the USA enrolled 157 cancer patients (156 women and 1 man) from November 1999 to May 2000. Table 1 gives the entry and exclusion criteria for this study. Of the 157 patients randomized into this study, 155 (99%) received at least one dose of study drug and were evaluable for safety, and 152 (97%) were evaluable for efficacy (modified intention-to-treat population).

Study design

This multicenter double-blind randomized study evaluated whether a fixed dose of pegfilgrastim was as safe and effective as multiple daily doses of filgrastim in patients receiving four cycles of myelosuppressive doxorubicin and docetaxel chemotherapy (60 mg/m^2 and 75 mg/m^2, respectively).

Eligible patients were randomized (using a central interactive voice-response system) 1:1 to one of two double-blind treatment groups: to receive either a single fixed-dose subcutaneous (s.c.) injection of pegfilgrastim 6 mg or daily s.c. injections of filgrastim 5 μg/kg/day. Patients were assigned to treatment groups using a permuted block randomization taking weight, prior chemotherapy exposure and global location as stratification factors. Patients received the same study drug in all cycles.

The sample size of the study was based on a noninferiority design, and the mean duration and standard deviation (SD) of severe neutropenia observed in the phase II study [13].

Study drugs

Pegfilgrastim is composed of the protein filgrastim to which a 20 kDa PEG molecule is covalently bound at the N-terminal residue.

Patients randomized to filgrastim were to receive a dose of 5 μg/kg/day, based on actual body weight, administered as a s.c. injection. Injections began ~24 h after chemotherapy and continued daily until an absolute neutrophil count (ANC) $\geq 10.0 \times 10^9$/l was documented after the expected nadir or for a maximum of 14 days, whichever occurred first.

Patients randomized to pegfilgrastim were to receive a fixed dose of 6 mg (0.6 ml of a 10 mg/ml solution) as a single s.c. injection on day 2 of each cycle, ~24 h after chemotherapy. This injection was followed by daily s.c. injections of placebo until a documented ANC $\geq 10.0 \times 10^9$/l after the expected nadir or for a maximum of 14 days, whichever occurred first. The placebo consisted of the vehicle solution for filgrastim.

Treatment procedures

On day 1 of each cycle, patients received an i.v. bolus of doxorubicin (60 mg/m^2) followed ~1 h later by a 1-h i.v. infusion of docetaxel (75 mg/m^2). Chemotherapy was repeated every 3 weeks for up to four cycles. Full-dose chemotherapy was started on day 1 of each cycle, which was day 22 of the previous cycle, only if a patient had an ANC $\geq 1.0 \times 10^9$/l and a platelet count $>100 \times 10^9$/l. A 25% dose reduction was permitted if patients experienced grade 3/4 nonhematopoietic toxicities, two grade 3/4 infectious episodes, or grade 4 thrombocytopenia.

Blood samples were collected for complete blood counts (cbc) with differential on days 1, 3 and 5–9 of each cycle, continuing daily until an ANC $\geq 2.0 \times 10^9$/l after the expected nadir, then twice weekly, and at 1 and 3 months follow-up. Serum samples for a clinical chemistry panel and antibody analysis were collected before premedication in each chemotherapy cycle and at the end of treatment. Serum samples for pharmacokinetic analysis were collected in cycle 1 only, on the same days as blood samples for cbc. Patients recorded their oral body temperature daily, and were monitored for adverse events throughout the study.

Efficacy measurements

The primary efficacy end point was the duration of grade 4 neutropenia (defined as ANC $<0.5 \times 10^9$/l) in cycle 1. The secondary efficacy end points were the duration of grade 4 neutropenia in each of cycles 2–4, and the depth of the ANC nadir in each of cycles 2–4. Incidence of febrile neutropenia and time to neutrophil recovery (ANC $\geq 2.0 \times 10^9$/l) were also assessed, as was the incidence of i.v. antibiotic administration and hospitalization.

Safety assessments

Safety was assessed by the incidence of adverse events, antibody formation and changes in laboratory values. Patients were monitored for the formation of specific antibodies against pegfilgrastim or filgrastim using both an immunoassay (BIACore® 3000) and a cell-based bioassay.

Table 1. Inclusion and exclusion criteria for the study

Entry criteria	Exclusion criteria
Age >18 years	Bilirubin > upper limit of normal; or aspartate transaminase and/or alanine transaminase >1.5 × upper limit of normal, concomitant with alkaline phosphatase >2.5 × upper limit of normal
Investigator diagnosis of high-risk stage II or stage III/IV breast cancer	Received systemic anti-infective treatment within 72 h of chemotherapy
Eastern Cooperative Oncology Group (ECOG) performance status ≤2	Radiation therapy within 4 weeks of randomization into this study
Chemotherapy naïve or adjuvant therapy only or only one chemotherapy regimen for metastatic disease	Prior bone marrow or stem cell transplantation
Absolute neutrophil count $\geq 1.5 \times 10^9$/l; platelet count $\geq 100 \times 10^9$/l	Total lifetime exposure to doxorubicin >240 mg/m^2 or epirubicin >600 mg/m^2
Serum creatinine <1.5 × upper limit of normal	

Statistical analysis

Treatment group differences in duration of grade 4 neutropenia were analyzed using 95% two-sided confidence intervals (CIs), calculated using bootstrap resampling stratified by previous chemotherapy and weight. Pegfilgrastim was to be considered noninferior to filgrastim if, in cycle 1, the upper limit of the two-sided 95% CI for the difference in mean duration of grade 4 neutropenia was <1 day. Even allowing for a drop-out rate of 20% in cycle 1, the sample size of the study provided a 95% power to reject the null hypothesis if the true mean duration of severe neutropenia of pegfilgrastim was within 1 day of that of filgrastim. For variables other than grade 4 neutropenia, analyses were based on conventional methods (i.e. assuming asymptotic normality) for calculating 95% CIs and employed no stratification. ANC nadir, a secondary end point, was predetermined to be analyzed with a 95% two-sided CI. The log transformation was used on the nadirs to satisfy the normality assumption.

In addition, exploratory analyses of the relationship between the duration of grade 4 neutropenia and body weight, prior chemotherapy and other demographic variables were performed. Rates of febrile neutropenia were analyzed per cycle and over the duration of the study. Rates of i.v. antibiotic administration and hospitalization over the duration of the study were summarized.

Because this study was a noninferiority design, the protocol called for the primary efficacy analyses to be performed on the subset of patients without deviations that had the potential to affect the end points. The results from these analyses did not differ materially from those reported in this paper for the modified intention-to-treat subset.

Results

Patients

One hundred and fifty-seven patients were randomized into this trial, 80 patients to pegfilgrastim and 77 patients to filgrastim. The mean ages were 52.1 (SD 9.2) and 52.8 (SD 11.5) years for the pegfilgrastim and filgrastim groups, respectively. The majority of patients were white. The two groups were balanced for other demographic factors and disease status at baseline (Table 2). Overall, 28% of patients had received prior chemotherapy and 26% had received prior radiotherapy, with no imbalances between groups. More than 90% of the patients initiated all four cycles of chemotherapy, and the total chemotherapy dose administered in each group was similar, with ~5% of patients having >25% dose reduction in any cycle. Ninety percent of patients received chemotherapy according to the planned schedule.

One hundred and fifty-five patients (99%) received at least one dose of assigned study drug and were included in the safety analysis. Three patients received the wrong study drug. Two patients randomized to filgrastim received pegfilgrastim and were analyzed in the pegfilgrastim safety subset. One patient randomized to pegfilgrastim received filgrastim and was analyzed in the filgrastim safety subset. Compliance with study drug administration was high, with only five patients (3%) recording a missed or incorrect dose.

One hundred and fifty-two patients (97%) were eligible for efficacy analysis of the primary end point. Two pegfilgrastim patients (3%) and four filgrastim patients (5%) withdrew from the study because of adverse events. Figure 1 illustrates the progression of patients through the study.

Table 2. Baseline demographic and disease status for patients evaluable for efficacy (n = 152)

Characteristic	Daily filgrastim arm (n = 75)	Single-dose pegfilgrastim arm (n = 77)
Age, years		
Mean (SD)	52.8 (11.5)	52.1 (9.2)
Range	30–74	31–75
Sex, n (%)		
Women	74 (99)	77 (100)
Race, n (%)		
Caucasian	73 (97)	75 (97)
Geographical location, n (%)		
Australia	12 (16)	10 (13)
Europe	53 (71)	55 (71)
USA	10 (13)	12 (16)
Prior chemotherapy, n (%)		
No	54 (72)	55 (71)
Prior radiotherapy, n (%)		
No	59 (79)	54 (70)
Baseline weight, kg		
Mean (SD)	72.8 (15.9)	73.5 (15.6)
Range	49–132	46–125
Baseline ANC, $\times 10^9$/l		
Mean (SD)	4.8 (1.9)	4.7 (1.7)
Disease stage at entry, n (%)		
Stage II	23 (31)	19 (25)
Stage III	20 (27)	21 (27)
Stage IV	32 (43)	37 (48)

ANC, absolute neutrophil count; SD, standard deviation.

Efficacy

The incidence of grade 4 neutropenia by cycle in the pegfilgrastim group was 84%, 57%, 56% and 51%, compared with 83%, 54%, 53% and 49% in the filgrastim group for cycles 1–4, respectively. The mean duration of grade 4 neutropenia was similar between treatment groups in all cycles (Table 3).

In cycle 1, the mean duration of grade 4 neutropenia for the pegfilgrastim group was 1.8 days compared with 1.6 days in the filgrastim group. The mean difference between filgrastim and pegfilgrastim was 0.23 days, with a 95% two-sided CI of –0.15 to 0.63 days. The prospective noninferiority criterion of 1 day was, therefore, excluded, and the study met its primary end point.

The duration of grade 4 neutropenia was shorter in later cycles in both treatment groups. The mean duration of grade 4 neutropenia for the pegfilgrastim group was 1.1, 1.1 and 1.0 days, and for the filgrastim group 0.9, 0.9 and 1.0 days in cycles 2, 3 and 4, respectively. In all these later cycles, the CIs indicated the comparability in mean duration of grade 4 neutropenia between patients receiving pegfilgrastim 6 mg and patients receiving daily

Table 3. Mean duration of grade 4 neutropenia in cycles 1–4

	Filgrastim, 5 µg/kg/day	Pegfilgrastim, fixed 6 mg	Difference between means[a] (95% CI)
Cycle 1			
No. of patients started	75	77	
Mean duration of grade 4 neutropenia, days (SD)	1.6 (1.1)	1.8 (1.4)	0.23 (–0.15 to 0.63)
Cycle 2			
No. of patients started	74	76	
Mean duration of grade 4 neutropenia, days (SD)	0.9 (1.0)	1.1 (1.2)	0.13 (–0.20 to 0.47)
Cycle 3			
No. of patients started	73	75	
Mean duration of grade 4 neutropenia, days (SD)	0.9 (1.1)	1.1 (1.2)	0.16 (–0.20 to 0.51)
Cycle 4			
No. of patients started	70	74	
Mean duration of grade 4 neutropenia, days (SD)	1.0 (1.3)	1.0 (1.1)	0.00 (–0.39 to 0.39)

[a]Differences calculated by subtracting the filgrastim mean from the pegfilgrastim mean.

filgrastim. The median number of daily filgrastim injections in cycles 1, 2, 3 and 4 was 11, 11, 11 and 10, respectively.

In an effort to determine whether the fixed dose of 6 mg pegfilgrastim provided adequate support for patients of all weights, the duration of grade 4 neutropenia in subsets of patients grouped by baseline weight (≤62 kg, >62 to ≤71 kg, >71 to ≤80 kg and >80 kg) was evaluated. Results from all cycles suggested that all weight groups were adequately supported (cycle 1 results are shown in Table 4).

Duration of grade 4 neutropenia was explored in subsets of patients defined by prior chemotherapy status. Although a non-significant trend was evident for patients who had received prior chemotherapy to have longer durations of grade 4 neutropenia, no indication of a difference in efficacy of the pegfilgrastim and filgrastim groups was demonstrated (data not shown).

Febrile neutropenia was defined as an ANC $<0.5 \times 10^9$/l with a coincidental oral equivalent temperature ≥38.2°C. Based on analysis of the laboratory and body temperature data, seven patients (9%) in the pegfilgrastim group and 11 patients (15%) in the filgrastim group experienced febrile neutropenia in cycle 1. Compared with cycle 1, the incidence of febrile neutropenia in later cycles was lower for both treatment groups. Over the entire study, 10 (13%) pegfilgrastim-treated patients experienced febrile neutropenia compared with 15 (20%) filgrastim-treated patients. The incidence of febrile neutropenia was not statistically different between pegfilgrastim and filgrastim, with a 95% CI for the observed –7% difference of –19% to 5%.

The median time of recovery to an ANC $>2.0 \times 10^9$/l in all cycles was 9 days from the day of chemotherapy administration for both the pegfilgrastim group and the filgrastim group (Figure 2). Within the pegfilgrastim group, the ANC and serum concentration of pegfilgrastim during cycle 1 were consistent with pegfilgrastim being cleared by a neutrophil-mediated mechanism, with sustained serum concentrations of pegfilgrastim observed during the period of neutropenia (Figure 3).

Rates of i.v. antibiotic administration (21% and 17%) and hospitalization (31% and 18%) for the filgrastim and pegfilgrastim groups, respectively, were generally consistent with the results obtained for the incidence of febrile neutropenia.

Safety

The safety profile of pegfilgrastim, assessed by adverse events, antibody formation, and changes in laboratory values, was similar to that of filgrastim. No patterns or trends indicative of pegfilgrastim toxicity were observed.

Table 4. Duration of grade 4 neutropenia (in days) in cycle 1, by weight

	Baseline weight, kg			
	46–≤62	>62–≤71	>71–≤80	>80–132
Filgrastim, 5 µg/kg/day				
n	21	19	17	18
Mean duration of grade 4 neutropenia, days (SD)	1.8 (1.2)	1.6 (1.3)	1.8 (0.7)	1.2 (1.1)
Pegfilgrastim, fixed 6 mg				
n	20	23	14	20
Mean duration of grade 4 neutropenia, days (SD)	1.6 (1.0)	2.3 (1.6)	1.7 (0.9)	1.7 (1.6)

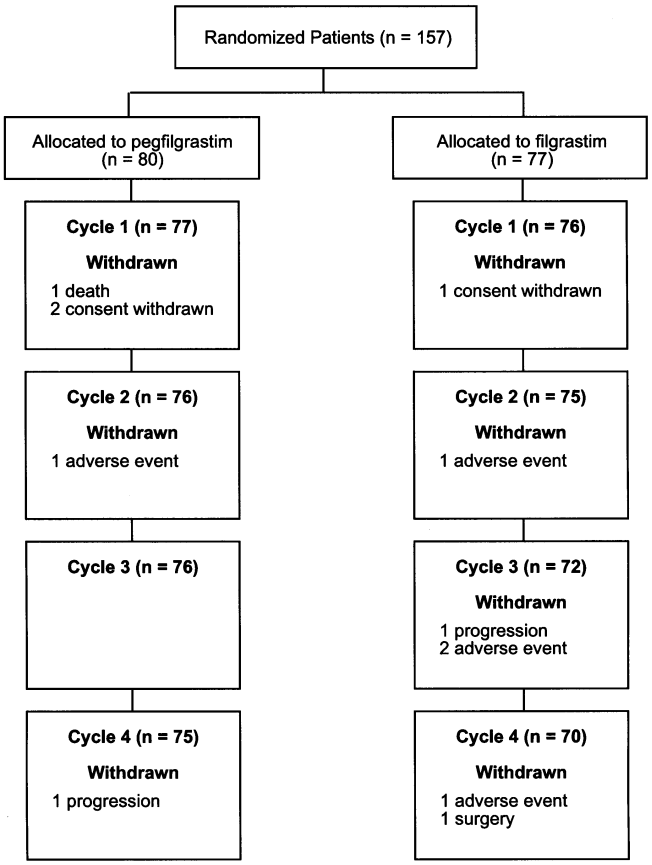

Figure 1. Disposition of patients in the trial.

All patients reported at least one adverse event. Most adverse events were attributable to complications of myelosuppressive chemotherapy or the primary disease. Forty-five of 79 pegfilgrastim patients (57%) and 44 of 76 filgrastim patients (58%) reported at least one adverse event that was considered by the investigator to be possibly related to the study drug. One patient in the filgrastim group died of adult respiratory distress syndrome (ARDS). In the filgrastim group, two serious adverse events (pneumonitis; and ARDS, bronchopneumonia and sepsis) were reported (on day 7 and day 16 of cycle 3, respectively). In the pegfilgrastim group, one patient had a serious adverse event (hypoxia and chest pain) on day 3 of cycle 2. No other serious events were considered by investigators to be possibly related to the study drug. The most frequently reported adverse event considered to be possibly related to the study drug by the investigator was bone pain (37% pegfilgrastim; 42% filgrastim). Bone pain was usually mild or moderate in severity, with only 1% and 8% of patients reporting severe bone pain in the pegfilgrastim and filgrastim groups, respectively. A fixed dose of pegfilgrastim was not observed to be associated with an increased incidence or severity of bone pain in patients with lower body weight (data not shown).

No patients developed neutralizing antibodies against either pegfilgrastim or filgrastim, and all patients recovered their ANC to $>1.0 \times 10^9$/l by the end of their final study chemotherapy cycle. As reported above, we observed expected transient neutropenia; the overall hematological profiles reflected those characteristic of patients receiving myelosuppressive chemotherapy. The incidence of grade 4 anemia (0% pegfilgrastim; 4% filgrastim) and grade 4 thrombocytopenia (0% pegfilgrastim; 1% filgrastim) was low. Transient reversible increases in alkaline phosphatase, lactate dehydrogenase and uric acid, without clinical sequelae, usually within the normal range, were observed, similar to those previously reported with filgrastim [7].

Discussion

Randomized trials have demonstrated the benefit of filgrastim, when used prophylactically for neutropenia induced by cytotoxic chemotherapy, in the reduction of: febrile neutropenia; the duration of grade 4 neutropenia; the depth of the neutrophil nadir; the number of hospitalizations; and antibiotic use [2–5, 14].

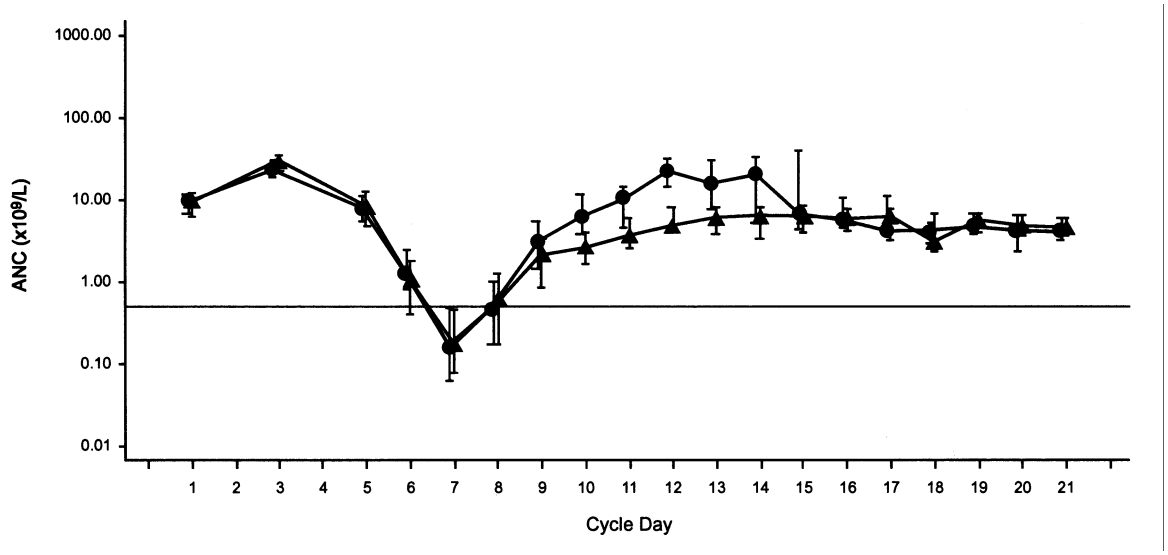

Figure 2. Median absolute neutrophil count (ANC) for cycle 1. Solid triangles represent pegfilgrastim 6 mg; solid circles represent filgrastim 5 μg/kg/day.

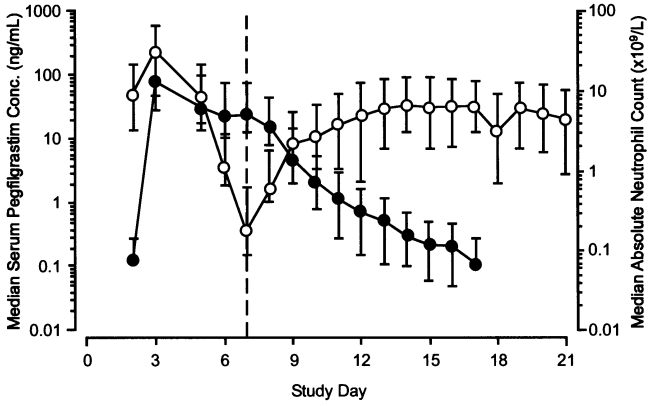

Figure 3. Median serum pegfilgrastim concentration (solid circles) and absolute neutrophil count (ANC) (open circles) in patients ($n = 73$) after a single 6 mg pegfilgrastim injection. Error bars show interquartile ranges. Dotted line indicates nadir.

Filgrastim has a short half-life and, therefore, requires daily administration. A longer-acting form would be a substantial advance in the management of chemotherapy-induced neutropenia and its consequences.

The current study demonstrates that a single fixed-dose injection of 6 mg pegfilgrastim per chemotherapy cycle is as safe and effective as daily injections of filgrastim for neutrophil support in patients being treated with a cytotoxic myelosuppressive chemotherapy regimen. This finding confirms previous phase II and phase III studies in breast and thoracic malignancies [12, 13, 15] that demonstrated the efficacy of pegfilgrastim (100 μg/kg) compared with filgrastim.

Pegfilgrastim was given as a single fixed dose of 6 mg in this study, and this dose supported rapid neutrophil recovery in a manner comparable to daily injections of filgrastim. Filgrastim is available in prefilled syringes and vials containing 300 or 480 μg of the drug. Although the approved labeling recommends a dosing regimen of 5 μg/kg/day to support standard-dose chemotherapy, it is common in clinical practice to administer the entire contents of the unit in a single injection for reasons of convenience and ease of dosing. A fixed dose would also be expected to be the clinical preference for the administration of pegfilgrastim. This study was designed to test the safety and efficacy of a fixed dose of pegfilgrastim compared with filgrastim, in a rigorous myelosuppressive setting. Six milligrams was selected based on pharmacokinetic and pharmacodynamic data from both computer modeling and observed results from patients treated in the previous phase II study in breast cancer [13, 16].

A potential problem regarding the fixed dose is that it might not offer heavier patients as complete clinical benefit due to a decreased overall per-kilogram dose. Evidence from this study suggests that the fixed dose would be equally efficacious in heavier patients; the relative durations of grade 4 neutropenia were comparable in heavier and lighter patients. An additional consideration was that a fixed dose might result in an altered safety profile in lighter patients. However, when evaluated both between treatment groups and within weight groups, the fixed dose of pegfilgrastim did not present any difference with respect to the incidence or severity of adverse events compared with filgrastim. This finding is not unexpected as filgrastim is commonly used as a fixed dose (either at 480 μg or 300 μg), and its safety profile and tolerability over a wide dose range is well documented.

This trial demonstrated that a single fixed dose of 6 mg of pegfilgrastim provides support to patients with chemotherapy-induced neutropenia in a manner similar to multiple daily doses of filgrastim. Importantly, the safety profile was not different from that of filgrastim. As such, a fixed dose of pegfilgrastim provides all the clinical benefits of filgrastim but with the advantage of once-per-cycle dosing. Once-per-cycle fixed-dose pegfilgrastim is expected to simplify the management of chemotherapy-induced neutropenia, and also provide significant quality-of-life benefits to oncology patients in the form of fewer injections.

Acknowledgements

Contributors: B.-B. Yang assisted with the pharmacokinetic studies; S. Bashir, L. R. Hill and J. Breddy assisted with the statistical analysis; and M. A. Foote with the writing of this manuscript. Financial support: this study was sponsored by Amgen Inc., Thousand Oaks, CA, USA.

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