Comparable efficacy and safety profiles of once-per-cycle pegfilgrastim and daily injection filgrastim in chemotherapy-induced neutropenia: a multicenter dose-finding study in women with breast cancer

F. A. Holmes1*, S. E. Jones2, J. O’Shaughnessy2, S. Vukelja1, T. George1, M. Savin1, D. Richards1, J. Glaspy3, L. Meza4, G. Cohen5, M. Dhami6, D. R. Budman7, J. Hackett8, M. Brassard8, B. B. Yang8 & B. C. Liang8

1US Oncology Research, Houston, TX; 2Baylor-Sammons Cancer Center, Dallas, TX; 3UCLA, Los Angeles, CA; 4Southwest Oncology Associates, Lafayette, LA; 5GBMC Healthcare, Baltimore, MD; 6Eastern Connecticut Hematology/Oncology Associates, Norwich, CT; 7Northshore University Hospital, Manhasset, NY; 8Amgen Inc., Thousand Oaks, CA, USA

Received 27 July 2001; revised 12 November 2001; accepted 26 November 2001

Background: Neutropenia is common in patients receiving myelotoxic chemotherapy. Pegfilgrastim, a sustained-duration filgrastim is a once-per-cycle therapy for prophylactic neutrophil support.

Patients and methods: Women, treated with four cycles of doxorubicin/docetaxel chemotherapy every 21 days, received pegfilgrastim or filgrastim 24 h after chemotherapy as a single subcutaneous injection per chemotherapy cycle (pegfilgrastim 30, 60 or 100 µg/kg) or daily subcutaneous injections (filgrastim 5 µg/kg/day). Safety, efficacy and pharmacokinetics were analyzed.

Results: The incidence of grade 4 neutropenia in cycle 1 was 95, 90 and 74%, in patients who received pegfilgrastim 30, 60 and 100 µg/kg, respectively, and 76% in patients who received filgrastim. Mean duration of grade 4 neutropenia in cycle 1 was 2.7, 2 and 1.3 days for doses of pegfilgrastim, and 1.6 days for filgrastim. The pharmacokinetics of pegfilgrastim were non-linear and dependent on both dose and neutrophil count. Pegfilgrastim serum concentration was sustained until the neutrophil nadir occurred then declined rapidly as neutrophils started to recover, consistent with a self-regulating neutrophil-mediated clearance mechanism. The safety profiles of pegfilgrastim and filgrastim were similar.

Conclusions: A single subcutaneous injection of pegfilgrastim 100 µg/kg provided neutrophil support and a safety profile comparable to daily subcutaneous injections of filgrastim during multiple chemotherapy cycles.

Key words: breast cancer, chemotherapy, filgrastim, neutropenia, pegylation, phase II clinical trial

Introduction

Patients with cancer receiving chemotherapy frequently develop neutropenia, which is the major dose-limiting toxicity of many chemotherapy regimens. Neutropenia is associated with many clinical sequelae, including febrile neutropenia, which often requires hospitalization and treatment with intravenous antibiotics. The benefits of filgrastim [recombinant methionyl human granulocyte colony-stimulating factor (r-metHuG-CSF)] in the setting of chemotherapy-induced neutropenia are well known (for a review, see Welte et al. [1]).

Filgrastim allows the timely delivery of cytotoxic chemotherapy at efficacious doses [2–4].

A sustained-duration form of filgrastim, pegfilgrastim, has been developed to decrease the number of injections to once per cycle of chemotherapy. Pegfilgrastim is a polyethylene glycol (PEG)-modified form of filgrastim. Non-clinical trials of pegfilgrastim in rodents and non-human primates have demonstrated sustained serum concentrations of pegfilgrastim after a single dose with a neutrophil response that closely correlates with pegfilgrastim serum concentration [5].

Pegfilgrastim appears to ‘self-regulate’ in serum [6]. The addition of the PEG molecule substantially reduces renal clearance of pegfilgrastim, resulting in neutrophil-mediated clearance as the primary mechanism of elimination. After chemotherapy, the serum concentration of pegfilgrastim is
sustained during neutropenia; pegfilgrastim is rapidly cleared as neutrophil counts recover, consistent with pegfilgrastim being cleared primarily by a neutrophil-mediated mechanism. This self-regulating property suggests that a single injection of pegfilgrastim may provide sufficient prophylactic neutrophil support with different durations of neutropenia, depending on the myelosuppressive characteristics of different chemotherapy regimens. Filgrastim, although also cleared by neutrophils, is primarily cleared by the kidney [7].

This dose-finding study was designed to investigate the efficacy, safety and pharmacokinetic profiles of various doses of once-per-cycle pegfilgrastim compared with daily filgrastim in women with breast cancer receiving multicycle myelosuppressive chemotherapy with doxorubicin and docetaxel, a regimen known to produce severe neutropenia.

**Patients and methods**

**Patients**

The institutional review boards of the participating centers approved the protocol and informed consent was obtained from all patients before any study-related procedures began.

Women were eligible for study entry if they met the following inclusion criteria: ≥18 years of age; diagnosis of high-risk (as defined by the investigator) stage II, III or IV breast cancer; Eastern Cooperative Oncology Group (ECOG) performance status ≤2; white blood cell (WBC) count ≥4 × 10^9/l; platelet count ≥150 × 10^9/l; adequate renal, hepatic and cardiac function. Eligible patients were chemotherapy naive, had received adjuvant therapy and/or had received one course of chemotherapy for metastatic disease. Patients were excluded from the study if their disease had progressed while receiving a taxane regimen, or they had undergone radiation therapy within 4 weeks of enrollment, a bone marrow or stem-cell transplantation or a total cumulative lifetime exposure to doxorubicin of >240 mg/m², or history of prior malignancy other than breast cancer.

A total of 152 patients received at least one dose of study drug and were evaluable for safety endpoints. Two patients who were evaluable for safety were excluded from the intention-to-treat analyses because of protocol deviations, resulting in 150 patients evaluable for efficacy endpoints.

**Study design and statistical analysis**

This study was a multicenter, randomized, dose-finding phase II study designed to compare the safety, efficacy and pharmacokinetics of once-per-cycle pegfilgrastim with daily filgrastim. Summary statistics were calculated for each endpoint. The two-sided 95% confidence intervals were calculated for the difference between each pegfilgrastim dose group and the filgrastim group for the mean duration of grade 4 neutropenia and mean time to absolute neutrophil count (ANC) recovery in each chemotherapy cycle. All significance tests were two-tailed with a nominal significance level (type I error rate) of 0.05.

To improve the precision of endpoint estimates, data were pooled from the same pegfilgrastim dose groups in the double-blind and open-label cohorts, after determining that no clinically meaningful differences were evident at any dose between the cohorts in the primary and secondary endpoints. Data pooling yielded four treatment groups (pegfilgrastim 30, 60 or 100 µg/kg, and filgrastim 5 µg/kg/day) for analysis. In the 30 µg/kg group, only cycle 1 analysis of efficacy is reported, as most of these patients received pegfilgrastim 60 µg/kg in later cycles.

**Study drugs**

Both filgrastim (Neupogen, Amgen Inc, Thousand Oaks, CA) and pegfilgrastim (Neulasta, Amgen Inc) are produced by recombinant DNA technology and are expressed in *Escherichia coli*. Pegfilgrastim comprises the protein filgrastim to which a PEG molecule is covalently bound at the N-terminal residue. Placebo consisted of the vehicle solution for filgrastim.

On day 2 of each chemotherapy cycle, ~24 h after chemotherapy completion, patients either received a single subcutaneous injection of pegfilgrastim or began daily subcutaneous injections of filgrastim that continued either for 14 days or until the ANC reached 10 × 10^9/l post-nadir, whichever occurred first.

**Treatment procedures**

Blood samples for chemistry panels were collected at screening, before each cycle of chemotherapy, and once weekly during cycle 1. Chemotherapy was administered on day 1 of cycle 1 and consisted of doxorubicin 60 mg/m² administered as an intravenous bolus followed by a 1-h intravenous infusion of docetaxel 75 mg/m². Treatment was repeated every 21 days for up to four cycles as long as full hematopoietic recovery occurred, defined as ANC >1 × 10^9/l and platelet count >100 × 10^9/l.

**Safety measurements**

The safety endpoint of this study was assessed in terms of adverse events and antibody formation. Serum was collected before study-drug administration to provide a baseline for the antibody screening assays and throughout the study at regular intervals. Serum samples were analyzed to detect the presence of immunoglobulin (Ig) G and IgM antibodies to pegfilgrastim and antibodies capable of neutralizing the biological effects of either pegfilgrastim or filgrastim. Changes in concomitant medicines, vital signs and laboratory tests were monitored.

**Efficacy measurements**

At screening and at baseline before administration of chemotherapy, blood samples were obtained for complete blood counts (CBC). CBC were measured daily beginning on day 2 of cycle 1 until ANC ≥20 × 10^9/l post-nadir, and three times a week thereafter for the duration of cycle 1, and three times a week during all subsequent cycles.

The primary efficacy endpoint of this study was the duration of grade 4 neutropenia, defined as the number of days in which the patient had an ANC <0.5 × 10^9/l during cycle 1 of chemotherapy. The secondary efficacy endpoints were the duration of grade 4 neutropenia during cycles 2–4, ANC profile and time to ANC recovery, defined as ANC ≥2 × 10^9/l after the expected ANC nadir. In addition, the rates of febrile neutropenia (defined as an oral or oral-equivalent temperature of ≥38.2°C concurrent with an ANC <0.5 × 10^9/l) were evaluated by treatment group.

**Pharmacokinetic measurements**

Blood samples for pharmacokinetic analysis were collected on day 2 of cycle 1, at time 0 (before injection of study drug), and 1, 2 and 4 h after injection of study drug, and then concurrently with samples collected for CBC in cycles 1 and 3.

Serum samples for cytokine measurements were analyzed using enzyme-linked immunosorbent assay (ELISA). Pharmacokinetic parameters for pegfilgrastim in cycle 1 were estimated using non-compartmental analysis of serum concentration–time data.
Results

Patients

A total of 154 women were randomized: 25 patients to filgrastim and 129 patients to pegfilgrastim. Mean [standard deviation (SD)] age was 50 (9) years in the filgrastim group and 50 (11) years in the pegfilgrastim group; most women were white. Stage IV disease was diagnosed in 40% and 23% of the filgrastim and pegfilgrastim patients, respectively; stage III disease in 36% and 38%, respectively; and stage II disease in 24% and 39%, respectively (Table 1). Most women were chemotherapy- (80% and 91%) and radiotherapy- (84% and 91%) naive in the filgrastim and pegfilgrastim treatment groups, respectively.

Two women randomized to the filgrastim group (one each to the 60 and 100 µg/kg groups) were excluded from the analysis of efficacy endpoints because of protocol deviations. Two additional women randomized to the pegfilgrastim group withdrew consent and terminated from the study before receiving any chemotherapy or study drug. Fourteen women (9% of all patients; one filgrastim, 13 pegfilgrastim) did not complete the study. Seven of these women withdrew for safety concerns: five patients treated with pegfilgrastim withdrew due to intolerable adverse events unrelated to pegfilgrastim, and two patients treated with pegfilgrastim withdrew because of disease progression also unrelated to pegfilgrastim. Of the five patients who experienced intolerable adverse events, one received pegfilgrastim 100 µg/kg and experienced worsening renal function. The remaining four patients were treated with pegfilgrastim 30 µg/kg (a sub-optimal dose) and had the following adverse events: one neutropenic fever; one myocardial infarction with dyskinesia; one decreased ejection fraction; one diarrhea, nausea and dehydration. One hundred and forty women completed the study: 24 women (96%) treated with filgrastim and 116 women (90%) treated with pegfilgrastim.

Study drug administration

The mean (SD) number of injections administered to patients treated with filgrastim was 10.6 (10) in cycle 1, 10.2 (10) in cycle 2, 10.4 (10) in cycles 3 and 11.6 (10.5) in cycle 4. Patients treated with pegfilgrastim received a single injection of study drug per chemotherapy cycle.

Chemotherapy administration

In patients receiving either pegfilgrastim 100 µg/kg or filgrastim 5 µg/kg daily, a median of four cycles of chemotherapy was administered. Chemotherapy was delivered on time in >90% of cycles in both the single-administration pegfilgrastim and the daily-administration filgrastim groups. The full planned dose of chemotherapy was delivered in >86% of chemotherapy cycles in both groups (Table 2).

---

Table 1. Summary of demographic and baseline characteristics for patients evaluable for efficacy

<table>
<thead>
<tr>
<th></th>
<th>Filgrastim 5 µg/kg</th>
<th>Pegfilgrastim 30 µg/kg</th>
<th>Pegfilgrastim 60 µg/kg</th>
<th>Pegfilgrastim 100 µg/kg</th>
<th>Total pegfilgrastim</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>25</td>
<td>19</td>
<td>60</td>
<td>46</td>
<td>125</td>
</tr>
<tr>
<td>Age (years) [mean (SD)]</td>
<td>50 (9)</td>
<td>51 (13)</td>
<td>51 (11)</td>
<td>49 (11)</td>
<td>50 (11)</td>
</tr>
<tr>
<td>Race [n (%)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>20 (80)</td>
<td>18 (95)</td>
<td>44 (73)</td>
<td>35 (76)</td>
<td>97 (78)</td>
</tr>
<tr>
<td>Black</td>
<td>2 (8)</td>
<td>1 (5)</td>
<td>5 (8)</td>
<td>6 (13)</td>
<td>12 (10)</td>
</tr>
<tr>
<td>Asian</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (3)</td>
<td>0 (0)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>2 (8)</td>
<td>0 (0)</td>
<td>5 (8)</td>
<td>3 (7)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (4)</td>
<td>0 (0)</td>
<td>4 (6)</td>
<td>2 (4)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>ANC (×10⁹/l) [mean (SD)]</td>
<td>5 (2.4)</td>
<td>5 (1.8)</td>
<td>5.1 (2.5)</td>
<td>4.8 (2.3)</td>
<td>5 (2.3)</td>
</tr>
<tr>
<td>Disease stage [n (%)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>6 (24%)</td>
<td>6 (32)</td>
<td>26 (42)</td>
<td>18 (38)</td>
<td>50 (39)</td>
</tr>
<tr>
<td>Stage III</td>
<td>9 (36%)</td>
<td>9 (47)</td>
<td>21 (34)</td>
<td>19 (40)</td>
<td>49 (38)</td>
</tr>
<tr>
<td>Stage IV</td>
<td>10 (40%)</td>
<td>4 (21)</td>
<td>15 (24)</td>
<td>11 (23)</td>
<td>30 (23)</td>
</tr>
</tbody>
</table>

Table 2. Percentage of patients with full chemotherapy dose delivered on time and at prescribed dose

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose on time (%)</th>
<th>Full dose delivered (doxorubicin) (%)</th>
<th>Full dose delivered (docetaxel) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filgrastim 5 µg/kg/day</td>
<td>98</td>
<td>88</td>
<td>86</td>
</tr>
<tr>
<td>Pegfilgrastim 100 µg/kg</td>
<td>96</td>
<td>88</td>
<td>86</td>
</tr>
</tbody>
</table>

*Reductions were defined as per decrease of chemotherapy dose compared with the first cycle of chemotherapy.
Safety

Adverse events

All patients reported adverse events; however, most were attributable to complications associated with myelosuppressive chemotherapy or disease progression. The most frequently reported cytokine-related adverse event was mild to moderate bone pain. The severity and duration of bone pain were similar for patients treated with pegfilgrastim and filgrastim. The overall incidence of bone pain was 35% in pegfilgrastim patients and 36% in filgrastim patients; most incidences were mild to moderate in severity. In the pegfilgrastim groups, 16%, 34% and 45% of subjects in the 30, 60 and 100 µg/kg dose groups, respectively, reported bone pain. In general, bone pain required no medication or was controlled with non-narcotic analgesia; a few patients (7% pegfilgrastim and 12% filgrastim) required narcotic analgesia.

Antibody formation

No evidence of neutralizing antibodies was observed. Consistent with this observation, ANC’s recovered to baseline values in all patients by the end of study.

Changes in medications, laboratory values and vital signs

As previously observed with filgrastim, transient, mild elevations, generally within the normal range, were observed in alkaline phosphatase, lactic dehydrogenase and uric acid levels in both treatment groups, and were without clinical sequelae.

Efficacy

Incidence and duration of grade 4 neutropenia for cycle 1

In chemotherapy cycle 1, grade 4 neutropenia was noted in 18 patients (95%) in the 30 µg/kg/cycle group, 54 patients (90%) in the 60 µg/kg/cycle group, 34 patients (74%) in the 100 µg/kg/cycle group and 19 patients (76%) in the filgrastim group. The mean (SD) duration of grade 4 neutropenia was 2.7 (1.3), 2 (1.2), 1.3 (1.1) and 1.6 (1.3) days for doses of 30, 60 and 100 µg/kg/cycle of pegfilgrastim and filgrastim 5 µg/kg/day, respectively. The 95% confidence limits for the difference in mean duration of grade 4 neutropenia between each pegfilgrastim dose group and filgrastim 5 µg/kg/day were (0.35, 1.93), (–0.21, 1.93) and (–0.81, 0.31) for the pegfilgrastim 30, 60 and 100 µg/kg dose groups, respectively. Patients treated with pegfilgrastim 30 µg/kg were at higher risk of inadequate neutrophil recovery as the lower limit of the confidence interval was greater than a zero day difference from the filgrastim 5 µg/kg/day treatment group.

The percentage of patients with 0–2 days of grade 4 neutropenia in cycle 1 was 38, 67 and 87% the pegfilgrastim 30, 60 and 100 µg/kg groups, respectively, and 88% in the filgrastim 5 µg/kg/day group (Table 3). In addition, the duration of grade 4 neutropenia ranged from 0 to 5 days in both the 30 and 60 µg/kg pegfilgrastim dose groups, compared with 0–4 days in the 100 µg/kg pegfilgrastim and 0–5 days in the filgrastim groups.

Duration of grade 4 neutropenia for cycles 2–4

As noted previously, most patients in the 30 µg/kg group were escalated to higher doses of pegfilgrastim in later cycles. In cycles 2–4, the incidence of grade 4 neutropenia ranged from 23% to 31% in pegfilgrastim 100 µg/kg patients, compared with 29% to 46% in the filgrastim patients. The duration of grade 4 neutropenia in cycles 2–4 ranged between 0 and 1 days in ≥98% of pegfilgrastim 100 µg/kg patients, compared with 86% in pegfilgrastim 60 µg/kg patients and ≥92% in filgrastim patients. In cycles 2 and 3, in both the filgrastim and the pegfilgrastim 100 µg/kg groups, all patients had a duration of grade 4 neutropenia of <3 days, while in the pegfilgrastim 60 µg/kg group 3% and 7% of patients had 3 days or more of grade 4 neutropenia in cycles 2 and 3, respectively. In cycle 4, a total of 4%, 7% and 2% of patients had ≥2 days of grade 4 neutropenia in the filgrastim, pegfilgrastim 60 µg/kg and pegfilgrastim 100 µg/kg groups, respectively.

ANC profiles

Compared with daily filgrastim, pegfilgrastim at a single dose of 100 µg/kg resulted in a similar ANC profile in cycle 1 (Figure 1) and subsequent cycles (Figure 2A). The ANC nadir occurred approximately on day 7 of each cycle. In cycle 1, the increase in ANC after the nadir differed between dose groups. Higher doses of pegfilgrastim produced a more rapid increase in the median ANC. Filgrastim patients, who could continue to receive filgrastim through day 14, exhibited a slight ‘overshoot’ during the ANC recovery. This dose effect is less evident in cycles 2–4, probably because these later cycles had less frequent ANC measurements (Figure 2A).

<table>
<thead>
<tr>
<th>No. of days</th>
<th>Filgrastim 5 µg/kg</th>
<th>Pegfilgrastim 30 µg/kg</th>
<th>Pegfilgrastim 60 µg/kg</th>
<th>Pegfilgrastim 100 µg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–2</td>
<td>88</td>
<td>37</td>
<td>67</td>
<td>87</td>
</tr>
<tr>
<td>≥3</td>
<td>12</td>
<td>63</td>
<td>33</td>
<td>13</td>
</tr>
</tbody>
</table>

*Values are percentage of patients.
Serum concentration of pegfilgrastim was correlated with ANC (Figure 2B). In all cases, with initiation of neutrophil recovery, serum levels declined, suggesting neutrophil-mediated clearance. Serum concentrations decreased to baseline values with recovery of ANC, over all cycles of chemotherapy.

**Time to ANC recovery**

The mean time to ANC recovery to ≥2×10^9/l for cycle 1 was 11 and 10.3 days in the pegfilgrastim 30 and 60 µg/kg groups, respectively, compared with 9.5 days in the pegfilgrastim 100 µg/kg group and 9.4 days in the filgrastim 5 µg/kg/day group. The mean time to ANC recovery was significantly longer in the pegfilgrastim 30 and 60 µg/kg/cycle dose groups, but not in the 100 µg/kg/cycle dose group, compared with filgrastim. The 95% confidence limits for the difference in mean time to ANC recovery between each pegfilgrastim dose group and filgrastim were (0.20, 3.34), (0.06, 1.66) and (−0.81, 0.93) for the pegfilgrastim 30, 60 and 100 µg/kg/cycle dose groups, respectively.

**Febrile neutropenia**

Febrile neutropenia was observed in 13 patients in cycle 1. In the pegfilgrastim 30, 60 and 100 µg/kg dose groups, four (21%), five (8%) and three (7%) patients, respectively, and in the filgrastim group, one patient (4%), experienced febrile neutropenia in cycle 1. Seven patients (12%) and five patients (11%) in the pegfilgrastim 60 and 100 µg/kg/cycle dose groups, respectively, and two patients (12%) in the filgrastim group, experienced febrile neutropenia in at least one cycle during the study. No statistically significant differences were observed between the incidence of febrile neutropenia in any pegfilgrastim dose group and the filgrastim group, either in cycle 1 or over all four cycles. Compared with cycle 1, the incidence of febrile neutropenia in later cycles was the same or modestly lower, but no consistent pattern was observed between treatment groups over time. This range validates the clinical observation that a single injection of pegfilgrastim administered at 100 µg/kg/cycle is similar to multiple injections of filgrastim 5 µg/kg/day.

**Pharmacokinetics**

A single dose of pegfilgrastim produced a sustained drug serum concentration compared with filgrastim (Figure 2B). Relative to the pegfilgrastim concentrations, median filgrastim serum concentration declined rapidly after subcutaneous administration. The pharmacokinetics of pegfilgrastim were non-linear at doses ranging from 30 to 100 µg/kg and were both dose and ANC dependent. The maximum pegfilgrastim serum concentration was achieved ~24 h after subcutaneous administration and was sustained until ANC nadir had occurred. As ANC recovered, pegfilgrastim serum concentration declined rapidly, consistent with a neutrophil-mediated clearance mechanism. The neutrophil-mediated clearance of pegfilgrastim was observed in cycles 1 and 3. Pegfilgrastim serum clearance decreased with increasing dose, suggesting saturation of clearance mechanisms at higher concentrations. As the dose increased from 30 to 100 µg/kg, the median average clearance estimated from the area under the concentration–time curve decreased from 26.4 to 6.7 ml/h/kg. Pegfilgrastim serum clearance appeared to be higher in cycle 3 than in cycle 1, possibly because of the expansion of neutrophil and neutrophil precursor mass after cycle 1.
Discussion

This study was designed to compare the safety, efficacy and pharmacokinetic profile of a single injection of pegfilgrastim with daily injections of filgrastim 5 µg/kg/day in patients receiving myelosuppressive chemotherapy and experiencing chemotherapy-induced neutropenia. The results of this phase II pilot study suggest that pegfilgrastim at 100 µg/kg, administered once per cycle of chemotherapy, provides a similar degree of hematopoietic support with respect to duration of grade 4 neutropenia compared with daily administration of filgrastim 5 µg/kg/day. Pegfilgrastim 100 µg/kg was found to be most comparable to filgrastim 5 µg/kg/day, as manifested by the similarities in ANC profile. Furthermore, both pegfilgrastim 100 µg/kg and filgrastim 5 µg/kg/day allowed >90% of chemotherapy doses to be delivered on time, and 100% of chemotherapy cycles to be delivered at the planned dose (at least 80% of the dose delivered in cycle 1). This level of dose intensity was achieved with a single dose of pegfilgrastim per chemotherapy cycle, whereas an average of ~11 injections of filgrastim were required when filgrastim was used in this chemotherapy regimen to support ANC recovery to >2 × 10⁹/l.

Figure 2. Median serum cytokine concentration–time and ANC–time profiles. (A) A semi-logarithmic plot of ANC over time. (B) A semi-logarithmic plot of cytokine serum concentrations over time. Conc., concentration.
Finally, pegfilgrastim was found to be as safe as filgrastim in this multicycle chemotherapy setting.

Of further interest were the pharmacokinetic results of this study, showing that pegfilgrastim has a ‘self-regulated’ clearance mechanism. Both filgrastim and pegfilgrastim are cleared by neutrophils, presumably after the binding to cognate receptors on the cell surface; however, filgrastim is also cleared by a renal mechanism, which results in a relatively short serum half-life of ~3 h. The addition of the PEG molecule to form pegfilgrastim effectively eliminates the renal clearance, and implicates a neutrophil-mediated mechanism as the primary clearance of the molecule. Clinically, this was noted in sustained concentrations of pegfilgrastim after subcutaneous injection, 24 h chemotherapy was administered and throughout the ANC nadir. At ANC recovery, pegfilgrastim clearance increased resulting in a rapid decrease of pegfilgrastim in the serum. Such clearance resulted in less ‘overshoot’ of ANC post-nadir, allowing for quicker establishment of baseline ANC before the next cycle of chemotherapy.

Neutropenia continues to be a dose-limiting concern for patients with cancer treated with cytotoxic chemotherapy, particularly because of the risk of associated clinical sequelae such as febrile neutropenia. The development and use of filgrastim has resulted in improvements in morbidity despite the use of intensive chemotherapy in patients harboring neoplastic disease. Moreover, with the advent of supportive agents such as filgrastim, chemotherapy-dose intensification and the avoidance of dose delay have been achieved with tolerable effects on patients receiving such myelosuppressive agents. Indeed, patients with non-Hodgkin’s lymphoma treated with combination cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) and cytokine support may have a greater overall survival than those patients treated similarly but without growth factor support [8].

Thus, this pilot study of pegfilgrastim provides evidence that a single injection of 100 µg/kg was similar to daily filgrastim in ANC support and safety in patients receiving a myelosuppressive chemotherapy regimen. The single administration of a growth factor with self-regulated clearance may be of substantial benefit, allowing for better compliance, uninterrupted therapy, convenience and potential cost-savings, simplifying the management of chemotherapy-induced neutropenia for both health-care workers and patients. Future phase III trials using pegfilgrastim should be optimized at a dose of 100 µg/kg.

Acknowledgements
The authors thank the study nurses and the patients for participating in this trial; Robert Hill for assistance with statistical analysis; Theresa Neumann, Diane Dunford and Beth Kin for assistance with study conduct; and Helen Wilfehr, Kathleen Pippo and MaryAnn Foote for assistance with writing of the manuscript. This work was supported by Amgen Inc., Thousand Oaks, CA, USA.

References