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

On behalf of the International Pegfilgrastim 749 Study Group†

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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/m2 and 75 mg/m2, 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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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) ≥10.0 × 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 ≥10.0 × 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/m²) followed −1 h later by a 1-h i.v. infusion of docetaxel (75 mg/m²). 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 ≥1.0 × 10^9/l and a platelet count ≥100 × 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 ≥2.0 × 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 × 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 ≥2.0 × 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.
The dose administered in each group was similar, with imbalances between groups. More than 90% of the patients initiated therapy and 26% had received prior radiotherapy, with no imbalances between groups. Overall, 28% of patients had received prior chemotherapy and 83% of patients received chemotherapy according to the planned schedule.

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 shorter in later cycles in both 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 single-dose filgrastim.
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 × 10⁹/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 × 10⁹/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 3. Mean duration of grade 4 neutropenia in cycles 1–4

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Filgrastim, 5 µg/kg/day</th>
<th>Pegfilgrastim, fixed 6 mg</th>
<th>Difference between means’ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients started</td>
<td>75</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>Mean duration of grade 4 neutropenia, days (SD)</td>
<td>1.6 (1.1)</td>
<td>1.8 (1.4)</td>
</tr>
<tr>
<td>Cycle 2</td>
<td>74</td>
<td>76</td>
<td>0.9 (1.0)</td>
</tr>
<tr>
<td>Cycle 3</td>
<td>73</td>
<td>75</td>
<td>0.9 (1.1)</td>
</tr>
<tr>
<td>Cycle 4</td>
<td>70</td>
<td>74</td>
<td>1.0 (1.3)</td>
</tr>
</tbody>
</table>

*Differs calculated by subtracting the filgrastim mean from the pegfilgrastim mean.

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

<table>
<thead>
<tr>
<th>Baseline weight, kg</th>
<th>Filgrastim, 5 µg/kg/day</th>
<th>Pegfilgrastim, fixed 6 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>46–≤62</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>&gt;62–≤71</td>
<td>19</td>
<td>23</td>
</tr>
<tr>
<td>&gt;71–≤80</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>&gt;80–132</td>
<td>18</td>
<td>20</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>Baseline weight, kg</th>
<th>Filgrastim, 5 µg/kg/day</th>
<th>Pegfilgrastim, fixed 6 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>46–≤62</td>
<td>1.8 (1.2)</td>
<td>1.6 (1.3)</td>
</tr>
<tr>
<td>&gt;62–≤71</td>
<td>1.6 (1.3)</td>
<td>1.8 (0.7)</td>
</tr>
<tr>
<td>&gt;71–≤80</td>
<td>1.8 (0.7)</td>
<td>1.2 (1.1)</td>
</tr>
<tr>
<td>&gt;80–132</td>
<td>1.2 (1.1)</td>
<td></td>
</tr>
</tbody>
</table>
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].
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.

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References


