

# Fixed-dose single administration of Pegfilgrastim vs daily Filgrastim in patients with haematological malignancies undergoing autologous peripheral blood stem cell transplantation

PB Staber, R Holub, W Linkesch, H Schmidt and P Neumeister

Division of Hematology, Medical University Graz, Graz, Austria

## Summary:

**Infectious complications are frequent events in patients undergoing high-dose cytotoxic chemotherapy with subsequent autologous peripheral blood stem cell transplantation (PBSCT). To evaluate whether a single subcutaneous injection of pegfilgrastim (6 mg) is as safe and effective as daily filgrastim (5 µg/kg/day), 60 consecutive autologous stem cell transplantations performed for various haematological malignancies have been analysed. In total, 24 patients undergoing 30 consecutive PBSCT received a single subcutaneous injection of 6 mg pegfilgrastim on day 5 after transplantation and were compared retrospectively with 30 patients receiving 5 µg/kg/day of filgrastim starting from day 7 post transplantation. The mean duration of grade 4 neutropenia in the pegfilgrastim and filgrastim groups was 8.3 and 9.5 days, respectively ( $P=0.047$ ). The results of the two groups were not significantly different for incidence of febrile neutropenia and toxicity profile. However, duration of febrile neutropenia (1.6 vs 3.0 days) and total days of fever (1.73 vs 4.1) were different ( $P=0.017$  and  $0.003$ , respectively), favouring the pegfilgrastim arm. Consequently, a higher incidence of transplants with documented infectious complications associated with the filgrastim group could be observed (56 vs 26%) ( $P=0.02$ ). A single injection of pegfilgrastim administered at day 5 post transplant shows comparable safety and efficacy profiles to daily injections of filgrastim.**

*Bone Marrow Transplantation* (2005) 35, 889–893.

doi:10.1038/sj.bmt.1704927

Published online 14 March 2005

**Keywords:** pegfilgrastim; filgrastim; autologous peripheral blood stem cell transplantation; PBSCT

The use of high-dose chemotherapy (HDC) followed by autologous haematopoietic stem cell transplantation is an

important treatment modality for patients with haematological malignancies that markedly improved the patients' outcome.<sup>1–5</sup> Haematologic toxicity associated with neutropenic complications is a major limiting toxicity of HDC. The duration of grade 4 neutropenia ( $ANC < 0.5 \times 10^9/l$ ) and neutrophil function deficiencies in the early post transplant period are correlated with the development of severe infectious complications, which have a major impact on overall morbidity and mortality.<sup>6</sup> Recombinant human granulocyte colony-stimulating factor (R-metHuG-CSF, filgrastim) reduces the risk of neutropenia and its complications by stimulating the production of neutrophil precursors and enhancing the function of mature neutrophils.<sup>7</sup> The administration of filgrastim in patients undergoing autologous transplantation reduced the duration of neutropenia and febrile neutropenia.<sup>8–10</sup> Filgrastim requires daily subcutaneous administration, since it has a plasma half-life of 3–4 h due to renal and neutrophil-mediated clearance.<sup>11,12</sup> Polyethylene glycol (PEG)-modification of filgrastim, pegfilgrastim, decreases renal clearance and increases plasma half-life.<sup>11</sup> Thus, only a single injection is required to achieve the same effect as multiple daily injections of filgrastim in patients receiving conventional chemotherapy. The potential benefit of a single injection includes a better patient compliance and increased convenience for both patients and healthcare professionals. In this study, we aimed to evaluate the efficacy and safety of a single fixed 6 mg dose of pegfilgrastim compared to daily administration of filgrastim in patients with haematological malignancies receiving HDC and autologous peripheral blood stem cell transplantation (PBSCT).

## Patients and methods

### Patient selection

We studied 60 consecutive autologous PBSCTs of 54 pretreated patients with haematological malignancies at the Medical University Graz, Austria from August 2002 to June 2004. During this period, supportive care, type of central venous catheter or empirical antibiotic regimens were not changed. Eligibility for PBSCT included to have an Eastern Cooperative Oncology Group performance status  $\leq 2$ , normal cardiac, pulmonary, hepatic and renal function prior to transplantation. Patients were excluded if

Correspondence: Dr P Neumeister, Division of Hematology, Leopold Auenbrugger University, Auenbruggerpl. 38, Graz A-8036, Austria; E-mail: peter.neumeister@meduni-graz.at  
Received 2 December 2004; accepted 31 January 2005  
Published online 14 March 2005

they had an active infection or had used antimicrobials within 72 h before chemotherapy administration. All individuals gave written informed consent and the protocol was approved by the hospital ethics committee.

### Conditioning and transplantation

PBSCT was performed on day 0 with unmanipulated peripheral blood stem cells that were harvested using cyclophosphamide (CY) and G-CSF before the start of the study. Preparative regimen for patients with Hodgkin's disease consisted of CY 1.5 g/m<sup>2</sup> once daily i.v. on days -6 to -3 (total dose 6 g/m<sup>2</sup>), etoposide 100 mg/m<sup>2</sup> twice daily i.v. on days -6 to -4 (total dose 600 mg/m<sup>2</sup>) and BCNU 300 mg/m<sup>2</sup> once daily i.v. on day -6 (CVB-regimen). In non-Hodgkin's lymphomas (NHL), HDC consisted of BCNU 300 mg/m<sup>2</sup> once daily i.v. (day -6), etoposide 100 mg/m<sup>2</sup> (days -5 to -2) given twice daily i.v. (total dose 800 mg/m<sup>2</sup>), and melphalan once daily i.v. 140 mg/m<sup>2</sup> (day -1) (BEAM-regimen). Acute leukaemias were treated with 12 Gy fractionated total body irradiation (days -6 to -4), and CY 60 mg/kg bw once daily i.v. (days -3 to -2) (total dose 120 mg/kg). Patients with multiple myeloma received 140–200 mg/m<sup>2</sup> melphalan once daily i.v. on day -2.

### Study drugs

Patients of the filgrastim (r-metHuG-CSF) group received daily subcutaneous injections of 5 µg/kg/day starting at day +7 after transplantation until an ANC > 10 × 10<sup>9</sup>/l. Patients treated with pegfilgrastim (peg-r-metHuG-CSF) received a single 6 mg subcutaneous injection on day +5 after transplantation.

### Efficacy and safety measurements

The primary end point of the study was duration of grade 4 neutropenia (ANC < 0.5 × 10<sup>9</sup>/l), which was defined as the number of days to achieve an absolute neutrophil count higher than 0.5 × 10<sup>9</sup>/l (first of at least 3 consecutive days). Secondary end points were incidence of febrile neutropenia (defined as ANC < 0.5 × 10<sup>9</sup>/l and temperature ≥ 38.2°C), duration of febrile neutropenia, duration of fever and incidence of documented infections (clinically or microbiologically documented infection with/without bacteraemia; definitions according to AGIHO/DGHO guidelines).<sup>13,14</sup> The safety end point of the study was the incidence of adverse events related to study medication.

### Statistical analysis

Differences between the experimental groups were tested by Fisher's exact test and the Mann-Whitney *U* test. A two-sided *P*-value of < 0.05 was considered to indicate statistical significance. No adjustment for multiple testing was performed.

## Results

### Patient characteristics

Table 1 summarises the baseline characteristics of the patients. 24 patients undergoing 30 consecutive PBSCT (six

patients had two consecutive PBSCT) receiving pegfilgrastim and 30 patients receiving filgrastim starting from day 7 post transplantation were compared retrospectively. Patients seemed generally well matched with respect to demographic and physical characteristics except baseline ANC and haemoglobin counts, which were in favour of the pegfilgrastim group. Nevertheless, no significant difference between both study arms regarding the first time point of developing grade 4 neutropenia (day post transplantation reaching ANC < 0.5 × 10<sup>9</sup>/l) could be observed. The mean number of CD34+ cells infused was not different between the groups.

### Study drug administration

Patients treated with pegfilgrastim received a single dose of 6 mg on day +5 after transplantation. The median number of subcutaneous injections administered to patients treated with filgrastim (5 µg/kg/day) was 7.

### Efficacy

**Duration of grade 4 neutropenia.** The day to reach ANC < 0.5 × 10<sup>9</sup>/l was similar in both groups (Table 1). The mean time to reach ANC > 0.5 × 10<sup>9</sup>/l was 8.3 days in the pegfilgrastim group compared to 9.5 days in patients treated with filgrastim (*P* = 0.047). The range was 5–14 days, respectively. Postnadir ANC recovery to 2.0 × 10<sup>9</sup>/l was achieved by all patients of both groups after a mean of 9.3 and 11 days, respectively (*P* = 0.04) (Table 2).

**Febrile neutropenia and duration of febrile neutropenia.** Febrile neutropenia was defined as an oral or oral-equivalent temperature of ≥ 38.2°C concurrent with an ANC less than 0.5 × 10<sup>9</sup>/l. The cumulative incidence of febrile neutropenia demonstrated no difference between the experimental groups. However, there was a difference regarding the mean number of febrile days during grade 4 neutropenia (= duration of FN) with 1.6 days in the pegfilgrastim and 3.0 days in the filgrastim group (*P* = 0.017). In addition, the

**Table 1** Demographic and baseline characteristics of patients

	Pegfilgrastim 6 mg	Filgrastim 5 µg/kg/day
No. of TX	30	30
No. of double TX	6	0
Sex (male/female)	13/11	21/9
<b>Diagnosis</b>		
Acute leukaemia	2	3
Multiple myeloma	19	12
NHL	7	14
Hodgkin's disease	2	1
Age (years) <sup>a</sup>	55.2 (21–71)	57.1 (30–71)
Baseline ANC (× 10 <sup>9</sup> /l) <sup>a</sup>	3.6 (1.25–9.1)	2.4 (0.76–6.1)
Day to ANC < 0.5 × 10 <sup>9</sup> /l <sup>a</sup>	2.4 (-1 to +5)	1.6 (-4 to +6)
Baseline platelet count (× 10 <sup>9</sup> /l) <sup>a</sup>	195 (54–387)	143 (29–337)
Baseline haemoglobin (g/dl) <sup>a</sup>	12.4 (8.3–17.6)	10.6 (7.7–13.2)
No. of infused CD34+ × 10 <sup>6</sup> /kg <sup>a</sup>	5.6 (2.2–13.4)	5 (1.9–19.8)

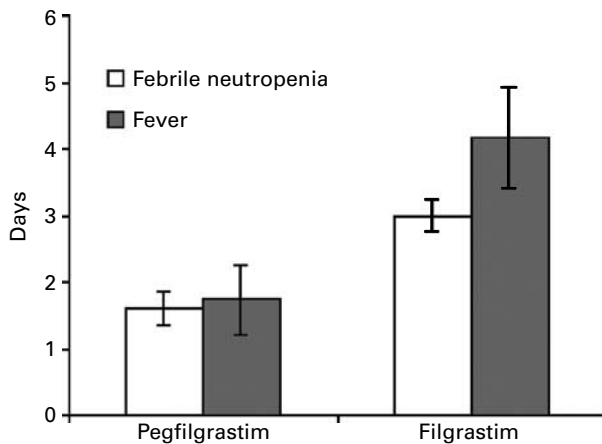
<sup>a</sup>Mean (range).

**Table 2** Efficacy/safety measurements

	Pegfilgrastim (n = 30)	Filgrastim (n = 30)	P
Duration of grad IV neutropenia (days) <sup>a</sup>	8.3 (5–14)	9.5 (5–14)	0.047
Duration of febrile neutropenia (days) <sup>a</sup>	1.6 (0–5)	3 (0–9)	0.017
Duration of fever (days) <sup>a</sup>	1.73 (0–5)	4.1 (0–16)	0.003
Incidence of febrile neutropenia	24 (80%)	23 (77%)	NS
Incidence of documented infections	8 (26%)	17 (56%)	0.02
Incidence of bone pain	6 (20%)	7 (23%)	NS

NS = not significant.

<sup>a</sup>Mean (range).



**Figure 1** Duration of febrile neutropenia and total days of fever. Error bars indicate standard error.

mean number of total days of fever (1.73 vs 4.1) were also in favour for the pegfilgrastim arm ( $P=0.003$ ) (Table 2, Figure 1).

#### Documented infections and microbiological surveillance

Documented infections according to AGIHO/DGHO criteria<sup>13,14</sup> occurred in 26.6% (8/30) transplantations in the pegfilgrastim group vs 56.6% (17/30) receiving filgrastim ( $P=0.02$ ). Mainly catheter related infections were more commonly seen in the filgrastim arm accounting for the described difference between the two groups. Further, microbiological surveillance data revealed more positive blood cultures in the filgrastim arm (24 of 18 vs 11 of 10 transplantations) with coagulase negative staphylococci being the most prominent pathogen in both groups (Table 2). As opposed to positive blood culture tests documented infections by coagulase negative staphylococci were only considered by two positive blood cultures. None of the patients developed documented fungal infections.

#### i.v. antibiotics and duration of hospitalisation

The mean duration of intravenous administration of antibiotics was 10.5 days (range 0–22) in the pegfilgrastim

and 11.4 days (range 4–23) in the filgrastim arm (NS,  $P=0.59$ ). Duration of hospitalisation from day 0 (day of transplantation) to discharge was 15.1 days (9–25) for pegfilgrastim and 16.3 days (11–23) for the filgrastim group (NS,  $P=0.125$ ).

#### Safety

Most adverse events (AE) were attributable to complications arising from myelo-suppressive chemotherapy or the primary disease. The only occurring AE considered to be cytokine related was mild to moderate bone pain. The overall incidence of bone pain was 20% (6/30) in pegfilgrastim patients and 23% (7/30) in filgrastim patients. In general, bone pain required no medication or was controlled with non-narcotic analgesia (Table 2).

#### Discussion

Patients with haematological malignancies undergoing HDC and subsequent autologous PBSCT experience a prolonged episode of neutropenia associated with high rates of neutropenic-related morbidity and occasional mortality. Most randomised trials using daily subcutaneous injections of G/M-CSF have shown to significantly shorten duration of neutropenia and hospitalisation<sup>9,10,15,16</sup> and possibly reducing costs.<sup>16,17</sup> The optimal timing of G-CSF administration is still under investigation. Two randomised studies demonstrated no significant differences in efficacy between early or delayed G-CSF administration (d1 vs d7<sup>18</sup> and d0 vs d3 vs d5<sup>19</sup>), but both reported cost savings with the delayed treatment. A PEG-conjugated filgrastim, pegfilgrastim, was recently synthesised and displayed a decreased plasma clearance with a resultant increase in half-life, thus making it almost entirely dependent on neutrophil receptor-mediated clearance.<sup>20</sup> This decreased plasma clearance potentially can translate into enhanced clinical efficacy and would be more convenient for patients and health care providers through its once per cycle administration. Clinical trials to test the pharmacokinetics, safety, and efficacy of a single dose pegfilgrastim compared to filgrastim in patients with non-small-cell lung cancer, breast cancer and lymphoma receiving conventional chemotherapy revealed a similar safety and efficacy profile.<sup>20–24</sup> One trial reported significantly less episodes of febrile neutropenia across all chemotherapy cycles for the pegfilgrastim arm.<sup>21</sup>

The present study reveals that a single injection of pegfilgrastim was at least equivalent to a mean of seven daily injections of filgrastim in all efficacy and safety end points evaluated. In accordance with the study of Bence-Bruckler,<sup>18</sup> our control arm received filgrastim at day 7. Due to the prolonged pharmacokinetic profile it seemed reasonable to initiate pegfilgrastim administration at day 5 assuming an average duration of grade 4 neutropenia of ~8 days.

Although we are aware of the limitations of a non-randomised study, the presented data are in keeping with current published literature comparing conventional filgrastim with pegfilgrastim. The largest trial comprised 310

stage II to IV breast cancer patients, who were randomly assigned to receive 5 µg/kg daily of filgrastim ( $n = 156$ ) or a single 100 µg/kg dose of pegfilgrastim ( $n = 154$ ) after chemotherapy.<sup>21</sup> The percentage of patients with febrile neutropenia was 18% in the filgrastim group and 9% in the pegfilgrastim arm ( $P = 0.29$ ). In our study, we were not able to demonstrate a significant difference in the incidence of febrile neutropenia. However, the duration of febrile neutropenia as well as the entire number of febrile days was profoundly reduced in the pegfilgrastim group (1.4 and 2.3 days, respectively), suggesting a potential therapeutical advantage over standard filgrastim. These results are further substantiated by the observation of a notable decrease of the mean duration of grade 4 neutropenia by 1.2 days in the pegfilgrastim group. The acceleration of neutrophil recovery may also account for the lower incidence of clinically or microbiologically documented infections including positive blood cultures in patients receiving pegfilgrastim.

The prolonged pharmacokinetic profile of pegfilgrastim has raised the concern that this novel agent might have a higher toxicity compared to filgrastim. The most commonly reported toxicities related to G-CSF were bone pain. In accordance with previous studies<sup>21–25</sup> of patients treated with conventional chemotherapy, bone pain was comparable in both arms, indicating similar overall toxicity profiles.

Together with the convenience of a single dosing and the reductions in the duration of neutropenia, duration of febrile neutropenia and occurrence of documented infections, this study provides further evidence that pegfilgrastim might have potential advantages over standard filgrastim. A fixed-dose pegfilgrastim should facilitate the management of aplasia following autologous stem cell transplantation and may offer significant benefits for patients and health care providers. Consequently, it may serve as an attractive alternative to a repetitive single G-CSF administration modus, particularly in thrombopenic patients experiencing a prolonged neutropenic episode. However, prospective randomised studies are warranted to corroborate these results.

## References

- Philip T, Armitage JO, Spitzer G *et al.* High-dose therapy and autologous bone marrow transplantation after failure of conventional chemotherapy in adults with intermediate-grade or high-grade non-Hodgkin's lymphoma. *N Engl J Med* 1987; **316**: 1493–1498.
- Crump M, Smith AM, Brandwein J *et al.* High-dose etoposide and melphalan, and autologous bone marrow transplantation for patients with advanced Hodgkin's disease: importance of disease status at transplant. *J Clin Oncol* 1993; **11**: 704–711.
- Vose JM, Anderson JR, Kessinger A *et al.* High-dose chemotherapy and autologous hematopoietic stem-cell transplantation for aggressive non-Hodgkin's lymphoma. *J Clin Oncol* 1993; **11**: 1846–1851.
- Attal M, Harousseau JL, Stoppa AM *et al.* A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. *N Engl J Med* 1996; **335**: 91–97.
- Lowenberg B, Verdonck LJ, Dekker AW *et al.* Autologous bone marrow transplantation in acute myeloid leukemia in first remission: results of a Dutch prospective study. *J Clin Oncol* 1990; **8**: 287–294.
- Kirk Jr JL, Greenfield RA, Slease RB *et al.* Analysis of early infectious complications after autologous bone marrow transplantation. *Cancer* 1988; **62**: 2445–2450.
- Welte K, Gabrilove J, Bronchud MH *et al.* Filgrastim (r-metHuG-CSF): the first 10 years. *Blood* 1996; **88**: 1907–1929 Review.
- Schmitz N, Dreger P, Zander AR *et al.* Results of a randomised, controlled, multicentre study of recombinant human granulocyte colony-stimulating factor (filgrastim) in patients with Hodgkin's disease and non-Hodgkin's lymphoma undergoing autologous bone marrow transplantation. *Bone Marrow Transplant* 1995; **15**: 261–266.
- Klumpp TR, Mangan KF, Goldberg SL *et al.* Granulocyte colony-stimulating factor accelerates neutrophil engraftment following peripheral-blood stem-cell transplantation: a prospective, randomized trial. *J Clin Oncol* 1995; **13**: 1323–1327.
- Linch DC, Milligan DW, Winfield DA *et al.* G-CSF after peripheral blood stem cell transplantation in lymphoma patients significantly accelerated neutrophil recovery and shortened time in hospital: results of a randomized BNLI trial. *Br J Haematol* 1997; **99**: 933–938.
- Molineux G, Kinstler O, Briddell B *et al.* A new form of Filgrastim with sustained duration *in vivo* and enhanced ability to mobilize PBPC in both mice and humans. *Exp Hematol* 1999; **27**: 1724–1734.
- Layton JE, Hockman H, Sheridan WP *et al.* Evidence for a novel *in vivo* control mechanism of granulopoiesis: mature cell-related control of a regulatory growth factor. *Blood* 1989; **74**: 1303–1307.
- Buchheid D, Bohme A, Cornely OA *et al.* Diagnosis and treatment of documented infections in neutropenic patients – recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). *Ann Hematol* 2003; **82** (Suppl. 2): S127–S132.
- Link H, Bohme A, Cornely OA *et al.* Antimicrobial therapy of unexplained fever in neutropenic patients – guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO), Study Group Interventional Therapy of Unexplained Fever, (DKG-German Cancer Society). *Ann Hematol* 2003; **82** (Suppl. 2): S105–117.
- Nademanee A, Sniecinski I, Schmidt GM *et al.* High-dose therapy followed by autologous peripheral-blood stem-cell transplantation for patients with Hodgkin's disease and non-Hodgkin's lymphoma using unprimed and granulocyte colony-stimulating factor-mobilized peripheral-blood stem cells. *J Clin Oncol* 1994; **12**: 2176–2186.
- Lee SM, Radford JA, Dobson L *et al.* Recombinant human granulocyte colony-stimulating factor (filgrastim) following high-dose chemotherapy and peripheral blood progenitor cell rescue in high-grade non-Hodgkin's lymphoma: clinical benefits at no extra cost. *Br J Cancer* 1998; **77**: 1294–1299.
- Schmitz N, Dreger P, Zander AR *et al.* Results of a randomised, controlled, multicentre study of recombinant human granulocyte colony-stimulating factor (filgrastim) in patients with Hodgkin's disease and non-Hodgkin's lymphoma undergoing autologous bone marrow transplantation. *Bone Marrow Transplant* 1995; **15**: 261–266.
- Bence-Bruckler I, Bredeson C, Atkins H *et al.* A randomized trial of granulocyte colony-stimulating factor (Neupogen)

- starting day 1 vs day 7 post-autologous stem cell transplantation. *Bone Marrow Transplant* 1998; **22**: 965–969.
- 19 Bolwell BJ, Pohlman B, Andresen S *et al*. Delayed G-CSF after autologous progenitor cell transplantation: a prospective randomized trial. *Bone Marrow Transplant* 1998; **21**: 369–373.
  - 20 Johnston E, Crawford J, Blackwell S *et al*. Randomized, dose-escalation study of SD/01 compared with daily filgrastim in patients receiving chemotherapy. *J Clin Oncol* 2000; **18**: 2522–2528.
  - 21 Holmes FA, O’Shaughnessy JA, Vukelja S *et al*. Blinded, randomized, multicenter study to evaluate single administration pegfilgrastim once per cycle *versus* daily filgrastim as an adjunct to chemotherapy in patients with high-risk stage II or stage III/IV breast cancer. *J Clin Oncol* 2002; **20**: 727–731.
  - 22 Green MD, Koelbl H, Baselga J *et al*. A randomized double-blind multicenter phase III study of fixed-dose single-administration pegfilgrastim *versus* daily filgrastim in patients receiving myelosuppressive chemotherapy. *Ann Oncol* 2003; **14**: 29–35.
  - 23 Vose JM, Crump M, Lazarus H *et al*. Randomized, multicenter, open-label study of pegfilgrastim compared with daily filgrastim after chemotherapy for lymphoma. *J Clin Oncol* 2003; **21**: 514–519.
  - 24 Holmes FA, Jones SE, O’Shaughnessy J *et al*. 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. *Ann Oncol* 2002; **13**: 903–909.
  - 25 Kubista E, Glaspy J, Holmes FA *et al*. Bone pain associated with once-per-cycle pegfilgrastim is similar to daily filgrastim in patients with breast cancer. *Clin Breast Cancer* 2003; **3**: 391–398.