

## Pegfilgrastim compared with Filgrastim after autologous hematopoietic peripheral blood stem cell transplantation

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**In order to assess the effect of Pegfilgrastim on the duration of neutropenia and clinical outcome of patients after autologous peripheral blood stem cell (PBSC) transplantation, we compared 20 consecutive patients with lymphoma or multiple myeloma receiving a single 6-mg dose of Pegfilgrastim on day 1 posttransplant to an historical control group of 60 patients receiving daily Filgrastim 5 µg/kg starting on day 1 posttransplant. The duration of neutropenia was similar in the Pegfilgrastim group compared with the control group. There were no differences in time to neutrophil, erythroid, or platelet engraftment nor in the incidence of fever and infections. The duration of antibiotic therapy, transfusion support, and time to hospital discharge were similar in the two groups. However, after initial hematopoietic reconstitution, we observed significantly higher values of lymphocytes (e.g.,  $1660 \pm 1000$  versus  $970 \pm 460$  on day 80,  $p = 0.0002$ ), neutrophils (e.g.,  $3880 \pm 2030$  versus  $2420 \pm 1500$  on day 25,  $p = 0.0004$ ), reticulocytes (e.g.,  $148,160 \pm 90,590$  versus  $87,140 \pm 65,920$  on day 25,  $p < 0.0001$ ), and platelets (e.g.,  $210,700 \pm 116,090$  versus  $150,240 \pm 58,230$  on day 55,  $p = 0.0052$ ) up to day 100 in the Pegfilgrastim group compared with the Filgrastim group. These observations had no impact on clinical outcome of the patients after day 30 due to the low incidence of infectious events after engraftment in autologous PBSC transplantation. We conclude that the effect of Pegfilgrastim administered on day 1 posttransplant is comparable to that of daily Filgrastim on initial hematopoietic reconstitution. The possibly superior effect of Pegfilgrastim on cell counts we observed after initial engraftment should be further tested in a prospective randomized trial. © 2006 International Society for Experimental Hematology. Published by Elsevier Inc.**

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High-dose chemotherapy followed by autologous hematopoietic stem cell transplantation (HCT) is a widely accepted treatment modality for several selected hematologic malignancies. Low neutrophil counts in the early posttransplant period facilitate the occurrence of severe infectious complications and have a significant impact on overall morbidity and mortality after autologous HCT [1–4]. Various reports have shown that recombinant hematopoietic growth factors such as granulocyte colony-stimulating factor (G-CSF) [5–12] or granulocyte-macrophage colony-stimulating factor (GM-CSF) [13] significantly reduce the time to neutrophil recovery following autologous peripheral blood stem cell (PBSC) transplantation. Moreover, these previous studies have shown that the use of these myeloid growth

factors significantly decreases number of bacterial infections, number of days on antibiotics, and duration of initial hospitalization.

Research investigations have shown that their modification by chemical addition of poly(ethylene glycol) can alter the pharmacokinetic and pharmacodynamic properties of various proteins to significantly increase the time the modified proteins remain effective in the circulation [14]. Molineux et al. have developed a form of Filgrastim modified by the addition of a linear pegylated (PEG) molecule of 20 kD covalently bound to the N-terminus showing a sustained duration of action in vivo [15]. Clinical studies have demonstrated that Pegfilgrastim was as safe and effective as daily Filgrastim in several settings [16–20]. Pegfilgrastim administered once per cycle after chemotherapy for non-small cell lung cancer (NSCLC) [21], breast cancer [16,17], or lymphoma [18,20] provided neutrophil support and presented a safety profile comparable to that of daily Filgrastim. Successful transplantation of PBSC mobilized

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by chemotherapy and a single dose of Pegfilgrastim has been reported in patients with multiple myeloma [19]. The ability of a single injection of Pegfilgrastim to improve neutrophil recovery following bone marrow transplantation has been illustrated in rhesus macaques [22]. Recently, a few articles [23,24] and abstracts [25,26] compared the administration of a single 6-mg dose of Pegfilgrastim with daily Filgrastim after autologous PBSC transplantation. However, in these studies, the two treatments were started on differing days posttransplant (i.e., day +3 versus day +5 [26], day +2 versus day +5 [25], day +1 versus days +1 or +4 [23], and day +5 versus day +7 [24]). In addition, the evolution of hematologic parameters after initial hematopoietic recovery is not known. We present here our experience with the use of Pegfilgrastim compared with Filgrastim, both started on day 1 posttransplant, with 100-day follow-up after autologous PBSC transplantation.

## Patients and methods

### Patients

Between May 2004 and November 2004, 20 consecutive autologous stem cell transplantation recipients with lymphoid malignancies were treated with Pegfilgrastim after transplantation. They were compared to a historical control group of 60 patients selected in our database of patients receiving an autologous PBSC transplant and daily Filgrastim starting on day 1 in the preceding 3 years. This control group was matched 3:1 with the study group on the basis of age, sex, diagnosis, disease status at time of transplant, transplantation number, and starting day of posttransplant G-CSF. Patient characteristics are given in Table 1. All patients gave written informed consent to analysis of their clinical data and this process was approved by the Ethics Committee of the University of Liège.

### PBSC collection and transplantation

Multiple myeloma patients were mobilized with cyclophosphamide 4.5 g/m<sup>2</sup> and G-CSF 5 µg/kg/d, and lymphoma patients with cyclophosphamide 4.5 g/m<sup>2</sup>, VP16 1.5 g/m<sup>2</sup>, and G-CSF. PBSC were harvested in all patients by leukapheresis as previously described [27,28] and stored without further manipulation in liquid nitrogen in 7.5% dimethylsulfoxide. Conditioning regimens consisted of cyclophosphamide (120 mg/kg) + total body irradiation (12 Gy) for low-grade lymphoma (n = 15), BCNU, Etoposide, Ara-C, Melphalan (BEAM) for high-grade lymphoma or Hodgkin's disease (n = 15), and Melphalan (200 mg/m<sup>2</sup>) for multiple myeloma (n = 50). On the day of transplantation, cells were rapidly thawed and infused through a central catheter.

### Growth factors

In the study group, Pegfilgrastim (Neulasta, Amgen, Thousand Oaks, CA, USA) was administered at a single intravenous dose of 6 mg on day 1 posttransplant. In the historical control group, Filgrastim (Neupogen, Amgen, Thousand Oaks, CA, USA) was administered at a dose of 5 µg/kg/d from day 1 posttransplant until the absolute neutrophil count (ANC) was  $\geq 1 \times 10^9/L$  for 3 days or  $\geq 10 \times 10^9/L$  for 1 day, whichever came first. In both groups,

**Table 1.** Patient characteristics

	Filgrastim	Pegfilgrastim	<i>p</i> value
Number of patients	60	20	
Age (Mean ± SD)	56 ± 9	54 ± 10	
Sex			
Males	41 (68%)	13 (65%)	0.7820
Females	19 (32%)	7 (35%)	
Disease			
NHL + HD	20 (30%)	10 (50%)	0.1824
MM	40 (70%)	10 (50%)	
Disease status			
CR	17 (28%)	9 (45%)	0.1680
Not in CR	43 (72%)	11 (55%)	
Prior autologous HCT			
Yes	19 (32%)	6 (30%)	0.8890
No	41 (68%)	14 (70%)	
CMV status			
CMV+	27 (45%)	16 (80%)	0.0065
CMV−	33 (55%)	4 (20%)	
Graft composition (Mean ± SD)			
CD34 <sup>+</sup> cells (×10 <sup>6</sup> /kg)	10.03 ± 6.25	7.16 ± 3.82	0.0575
CFU-GM (×10 <sup>4</sup> /kg)	281.21 ± 258.70	232.12 ± 27.11	0.7968

NHL, Non-Hodgkin's lymphoma; HD, Hodgkin's disease; MM, multiple myeloma; CR, complete remission.

additional doses of Filgrastim were given when the ANC fell below  $1 \times 10^9/L$  at any time before day 100 posttransplant.

### Clinical management

Until engraftment, patients were kept in laminar air flow rooms and received chlorhexidine mouthwashes. Patients also received acyclovir (250 mg/m<sup>2</sup> b.i.d. intravenously and then orally as soon as feasible until day 40), oral antifungal prophylaxis with either 400 mg itraconazole or 400 mg fluconazole until day 40, and aerosolized pentamidine until day 120. All patients were managed with a totally implanted Port-A-Cath catheter (Braun, Melsungen, Germany) that remained in place at least until 1 year posttransplant. In case of fever above 38.3°C once or above 38°C on three consecutive measurements, empirical antibiotic therapy was started with a combination of cefepim + amikacin [29]. Patients were weekly screened for cytomegalovirus (CMV) by polymerase chain reaction (PCR). Preemptive therapy with ganciclovir (10 mg/kg intravenously thrice weekly) was initiated after a positive PCR and discontinued after two consecutive negative results. We used the definitions of the Infectious Diseases Working Party of the European Bone Marrow Transplant Group (EBMT) for diagnosis of bacteremia, fungemia, varicella-zoster virus infections, CMV infection, or disease [30]. Fever of unknown origin was defined as fever alone without clinical sign or bacteriologic documentation.

Complete blood counts were determined in an Advia cell counter (Bayer, Tarrytown, NJ, USA). Red blood cell (RBC) and platelet transfusions were given when the hemoglobin or platelet count were below 8 g/dL or  $15 \times 10^9/L$ , respectively.

### Statistical analyses

Unpaired and paired Student's *t*-tests as well as two-way analysis of variance were used to compare biologic parameters in the two groups. Welch's correction was used in case of unequal variance.

Number of transfusions in the two groups was compared using Mann-Whitney *U*-tests. Times to hematopoietic recovery were studied by life table analyses and Wilcoxon rank tests were used for comparisons between groups. Clinical outcome parameters were analyzed by Chi-square tests. Statistical analyses were carried out with Graphpad Prism (Graphpad Software, San Diego, CA, USA).

**Results**

*Hematopoietic recovery*

There was no significant difference in initial neutrophil engraftment between the two groups. Time to reach an ANC of 0.5 (Fig. 1) or  $1 \times 10^9/L$  or the number of days with neutropenia (Table 2) were similar in the two groups. Similarly, no difference was seen between the two groups for time to unsupported platelet count  $\geq 20$  or  $100 \times 10^9/L$  or the number of platelet transfusions (Table 2). There was also no significant difference in time to 1% reticulocytes or the number of red cell units transfused (Table 2).

After initial hematopoietic recovery, several differences between the groups became apparent. When significant, these differences always consisted in the Pegfilgrastim group showing higher counts compared with the Filgrastim group. The neutrophil count (day 25:  $3880 \pm 2030$  versus  $2420 \pm 1500$ ;  $p = 0.0004$ ) remained significantly higher in the study group between days 14 and 30 (Fig. 2), as did the lymphocyte count (day 80:  $1660 \pm 1000$  versus  $970 \pm 460$ ;  $p = 0.0002$ ) between days 56 and 90 (Fig. 2), the monocyte count between days 21 and 24, reticulocytes (day 24:  $148,160 \pm 90,590$  versus  $87,140 \pm 65,920$ ;  $p < 0.0001$ ) between days 17 and 42 (Fig. 2), and the platelet count (day 56:  $210,700 \pm 116,090$  versus  $150,240 \pm 58,230$ ;  $p = 0.0052$ ) between days 35 and day 90 (Fig. 2), respectively.

After the initial hematopoietic recovery and up to day 100, a total of three supplementary doses of Filgrastim

**Table 2.** Hematological recovery after transplantation

	Filgrastim	Pegfilgrastim	<i>p</i> value
Days to $0.5 \times 10^9/L$ neutrophils (median)	9	8	0.2281
Days to $1.0 \times 10^9/L$ neutrophils (median)	9	9	0.1620
Days to 1% reticulocytes (median)	15	13	0.1416
Days to last RBC transfusion (median)	8	7	0.6285
Days to $20 \times 10^9/L$ platelets (median)	9	9	0.6510
Days to $100 \times 10^9/L$ platelets (median)	31	20	0.4206
Days to last platelet transfusion (median)	7	6	0.5428
Number of G-CSF injections*	$10.7 \pm 1.7$	1	
Number of additional G-CSF injections†	$0.4 \pm 0.9$	$0.2 \pm 0.4$	0.2513
Number of red blood cell transfusions	$0.9 \pm 1.6$	$1.1 \pm 1.6$	0.5542
Number of platelet transfusions	$1.0 \pm 1.7$	$1.2 \pm 1.8$	0.7142

\*Number of injections until full neutrophil engraftment (see Methods).

†Number of injections for secondary neutropenia after initial neutrophil engraftment.

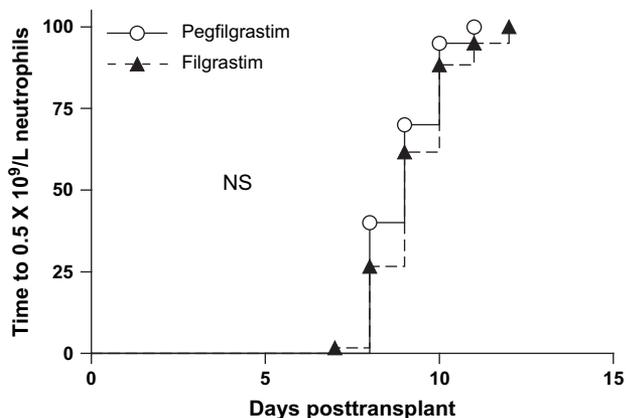
had to be administered to three patients in the Pegfilgrastim group ( $0.15 \pm 0.37$  per patient) and a total number of 24 doses to 20 patients in the control group ( $0.40 \pm 0.94$  per patient; not significant).

*Infections*

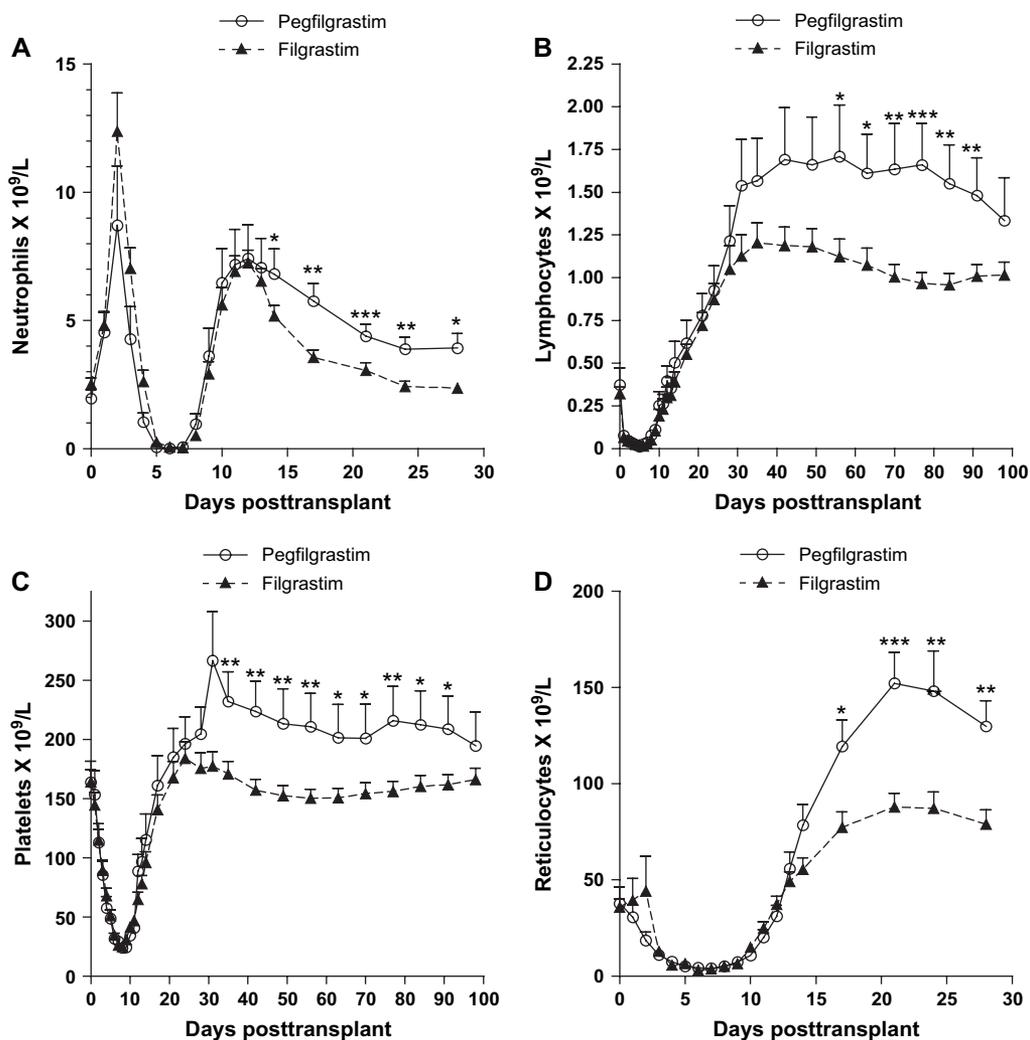
Clinically relevant infections occurring within 100 days posttransplant in the two groups are summarized in Table 3. There was no difference between the two groups for the overall incidence of infection, nor for specific rates of bacteremia, other bacterial infections, fungal infections, or zoster infections. The number of patients with CMV infection was higher in the study group, but this was only due to the larger proportion of CMV seropositive patients in this group compared to the control group ( $p = 0.0065$ ). Finally, there was no difference for the number of days with fever, days on antibiotics, days on amphotericin B, or duration of hospitalization. The cost of G-CSF until engraftment was  $1237 \pm 277$  €/patient with Filgrastim versus  $1207$  €/patient with Pegfilgrastim ( $p = 0.6210$ ).

**Discussion**

High-dose chemotherapy followed by autologous HCT is widely used in the treatment of patients with multiple myeloma and lymphoma. Severe and life-threatening infections complicating the profound and prolonged myelosuppression inevitably induced by high-dose chemotherapy remain a major factor of morbidity and mortality in patients undergoing autologous HCT [3,4]. The use of G-CSF after



**Figure 1.** Kaplan-Meier plot of time to  $0.5 \times 10^9/L$  neutrophils in the Pegfilgrastim group compared with the Filgrastim group.



**Figure 2.** Neutrophil (A), lymphocyte (B), platelet (C), and reticulocyte (D) counts after transplantation in the Pegfilgrastim group compared with the Filgrastim group. \* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$ .

autologous bone marrow transplantation has been shown to shorten the duration of severe neutropenia and thereby to reduce the risk of infections [1,2,31]. Compared to transplantation of bone marrow, autologous infusion of PBSC is associated with a reduced period of neutropenia, fewer infectious complications, and shorter duration of hospitalization [32]. Several authors have reported that G-CSF can reduce the duration of early severe neutropenia by a few days to 1 week after high-dose chemotherapy and autologous transplantation of PBSC, which may then lead to a decreased incidence of infectious complications, reduced use of antibiotics, and shorter duration of hospitalization [5–12]. However, the duration of G-CSF action is limited by its removal from the body by two mechanisms. The first mechanism is thought to be mediated by G-CSF receptors (receptor-mediated clearance), predominantly on neutrophils [33–35]. The second process is likely the result of renal clearance [34,35]. A new form of Filgrastim, modified

by the addition of PEG, has been produced. A single dose of Pegfilgrastim results in sustained drug concentration in serum [17,20,22] thanks to the poly(ethylene glycol) modification of Filgrastim that causes decreased renal clearance of the protein [36].

Molineux et al. [15] demonstrated that a single injection of Pegfilgrastim produced significantly elevated neutrophil counts for 5 days in hematologically normal mice or for 9 to 10 days in normal human volunteers. In neutropenic mice, its effect was prolonged for at least 9 days and produced a significant reduction in the duration of chemotherapy-induced neutropenia. Johnston et al. [21] demonstrated that a single injection of Pegfilgrastim in NSCLC patients receiving chemotherapy was as safe and effective on ANC and CD34<sup>+</sup> cell mobilization as daily Filgrastim. This efficacy and safety profile was confirmed by Holmes et al. [16,17] in woman with breast cancer receiving chemotherapy. Vose et al. [18] illustrated similar effects of

**Table 3.** Infectious complications after transplantation

	Filgrastim	Pegfilgrastim	<i>p</i> value
Duration of hospitalization after transplant	15.4 ± 5.8	14.5 ± 3.3	0.4991
Days with fever	2.3 ± 2.4	2.7 ± 2.3	0.5140
Days on IV antibiotics	8.4 ± 5.9	8.7 ± 5.9	0.8495
Days on IV amphotericin B	1.7 ± 5.1	2.6 ± 5.6	0.5068
Number of patients with possible infection (Fever of unknown origin)	18 (30%)	8 (40%)	0.3857
Number of patients with bacteremia	11 (18%)	7 (35%)	0.1221
Number of patients with other bacterial infection	24 (40%)	7 (35%)	0.4082
Number of patients with fungal infection	1 (2%)	1 (5%)	0.4082
Number of patients with CMV infection	9 (15%)	9 (45%)	0.0053
Number of patients with CMV infections among CMV+ patients	9 (33%)	9 (56%)	0.1409
Number of patients with CMV disease	1 (2%)	0 (0%)	0.5612
Number of patients with CMV disease among CMV+ patients	1 (3%)	0 (0%)	0.4360
Number of patients with Zoster infection	4 (6%)	0 (0%)	0.2360

Pegfilgrastim compared with daily Filgrastim in lymphoma patients undergoing salvage chemotherapy.

Farese et al. [22] examined the ability of a single injection of Pegfilgrastim to significantly improve neutrophil recovery following bone marrow transplantation in rhesus macaques and showed that the stimulation of granulopoiesis was equivalent to that observed with Filgrastim. A few studies have been conducted in patients undergoing PBSC transplantation. Soussain et al. [37] showed in 15 patients that a fixed 6-mg dose of Pegfilgrastim on day +3 was safe and effective. Musso et al. [25] observed that neutrophil engraftment, duration of hospitalization, and duration of intravenous antibiotics were similar in five patients receiving 6 mg Pegfilgrastim on day +2 and five other patients treated with daily Filgrastim from day +5. Musto et al. [26] demonstrated that 6 mg Pegfilgrastim on day +3 and daily Filgrastim from day +5 (11 patients in both groups) had comparable safety and efficacy profiles. Neutrophil engraftment occurred 2 days earlier with Pegfilgrastim, corresponding to the delay in initiating the two treatments. Jagasia et al. [23] confirmed that a single 6-mg dose of Pegfilgrastim on day +1 appeared safe and accelerated neutrophil engraftment comparable to daily Filgrastim started on day +1 or +4 (38 patients in each group). However, these authors did not compare the clinical outcome of patients receiving Pegfilgrastim with that of patients receiving Filgrastim. Staber et al. [24] showed that a single 6-mg dose of Pegfilgrastim on day +5 reduced the duration of grade 4 neutropenia, the duration of febrile

neutropenia, and the number of days of fever compared with daily Filgrastim started on day +7 (30 patients in each group).

However, in all these studies the two treatment modalities were started on differing days posttransplant (i.e., day +3 versus day +5 [26], day +2 versus day +5 [25], day +1 versus days +1 or +4 [23], and day +5 versus day +7 [24]). Our study compared 20 consecutive patients receiving Pegfilgrastim at a single dose of 6 mg on day +1 after transplantation with a historical control group of 60 patients receiving Filgrastim at a daily dose of 5 µg/kg also starting on day +1 posttransplant. The kinetics of early hematopoietic recovery was quite similar in the two groups, including neutrophil, erythroid, and platelet reconstitution. There was no more use of additional G-CSF doses after initial hematopoietic recovery in the Pegfilgrastim group compared with the Filgrastim group. No difference was observed between the two groups for infectious events. Although we observed significantly more CMV infections in the group of patients receiving Pegfilgrastim, this was only due to a higher proportion of CMV-seropositive patients in this group. Our study had a similar design to the Jagasia study [23], although in that study, an unknown proportion of the patients started Filgrastim on day +4. We achieved similar results for neutrophil recovery but other comparative data were not available in the Jagasia study [23].

Previous trials comparing Pegfilgrastim with Filgrastim outside of the transplant setting studied hematopoietic recovery after standard chemotherapy given in repeated cycles at intervals shorter than 4 weeks. Studies conducted in autologous transplant recipients only evaluated the impact of Pegfilgrastim on the primary hematopoietic recovery after autologous PBSC transplantation. Therefore, the evolution of blood cell counts could never be observed beyond day 30 postchemotherapy. In our study, a longer follow-up of 100 days posttransplant could be obtained. This may explain why we are the first to report a significant difference in the evolution of blood cell parameters in favor of the patients receiving Pegfilgrastim compared with those receiving Filgrastim. Indeed, we observed that neutrophil, lymphocyte, monocyte, reticulocyte, and platelet counts, although quite similar initially, were significantly higher in the group of patients receiving Pegfilgrastim during various periods of time after initial hematopoietic recovery. This took place despite a trend toward fewer CD34<sup>+</sup> cells transplanted in the Pegfilgrastim group. One could speculate that this would suggest broader effects of Pegfilgrastim on progenitor cell recovery but this remains to be demonstrated. However, this discrepancy did not translate into differences in clinical outcome, probably because most infections occurred in the early period of neutropenia. This apparently superior effect on cell counts of Pegfilgrastim over Filgrastim should be confirmed in prospective randomized trials that should also address the question of cost-effectiveness of Pegfilgrastim in this setting. Musso et al. [25] also suggested that Pegfilgrastim

administration could result in significant time savings for staff by reducing the number of drug administrations. With the convenience of a single-dose administration, Pegfilgrastim could become the future standard of care after autologous PBSC transplantation if its efficacy and cost can be proven to be at least equivalent to Filgrastim.

In our study, the cost of G-CSF was quite similar with Pegfilgrastim and Filgrastim. However, some studies have shown that postponing the initiation of G-CSF administration until day 5 or 6 posttransplant would not produce significant delays in neutrophil recovery [12,38,39]. Moreover, early discontinuation of G-CSF as soon as white blood cells reach a value of 1000/ $\mu$ L or neutrophils reach a value of 500/ $\mu$ L for 2 days after autologous hematopoietic stem cell transplantation is now being considered by some [40]. This would reduce the cost of Filgrastim administration and render Pegfilgrastim more expensive, unless a lower dose could do the job. However, in clinical practice, translating later initiation of Filgrastim treatment into lesser use of G-CSF is not straightforward. In the studies that compared daily Filgrastim with single-dose Pegfilgrastim, the number of Filgrastim doses ranged from seven when Filgrastim was started on day +7 [24] to 12 [26] or approximately 10 [25] when Filgrastim was started on day +5, approximately 8 to 11 when Filgrastim was started on day +1 or +4 [23], and 10.7 in our study in which Filgrastim was started on day +1. Therefore, initiating Filgrastim administration on day +5 does not automatically lead to fewer doses used compared with initiation on day +1. Prospective randomized studies that compare Pegfilgrastim with Filgrastim, ideally started on the same day, are warranted.

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