Phase II study of a single pegfilgrastim injection as an adjunct to chemotherapy to mobilize stem cells into the peripheral blood of pretreated lymphoma patients

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Background and Objectives. The aim of this study was to evaluate the efficacy of pegfilgrastim, in combination with salvage chemotherapy, in mobilizing CD34+ stem cells into the peripheral blood of pretreated lymphoma patients.

Design and Methods. This was an open-label phase II study including 25 pretreated patients (Hodgkin's disease=4; aggressive non-Hodgkin's lymphoma=21). The primary end-point of the study was the successful mobilization of a target cell dose of 2×10^6 CD34+ cells/kg in lymphoma patients receiving ifosfamide, epirubicin and etoposide (IEV) chemotherapy and a fixed dose (6 mg) of pegfilgrastim given as single subcutaneous injection.

Results. Following chemotherapy, all patients had grade 4 neutropenia that lasted a median of 1.5 days (1-3). Pegfilgrastim treatment was well tolerated and only 2/25 patients required pain-control medication. CD34+ cells were mobilized in all patients. The median (range) peak value of peripheral blood CD34+ cells after IEV chemotherapy and pegfilgrastim was 141×10^6/L (12.8-386) and occurred almost invariably on day +14 (13-16). Twenty-three of the 25 patients underwent a single standard volume leukapheresis to collect a median of 8.7×10^6 CD34+ cells/kg (1.78-17.3). Twenty four/25 patients (96%) reached the target cell dose of 2×10^6 CD34+ cells/kg. High concentrations of circulating CD34+ cells (> 50×10^6/L) were observed for several days after the achievement of the peak value. All the study patients were transplanted with their pegfilgrastim-mobilized CD34+ cells and showed a rapid and sustained engraftment after high-dose chemotherapy.

Interpretation and Conclusions. Our results show that pegfilgrastim as an adjunct to chemotherapy is a predictable and highly effective mobilization regimen in pretreated lymphoma patients.

Key words: CD34+ cells, mobilization, filgrastim, pegfilgrastim, autologous stem cell transplantation.

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Although advanced stage Hodgkin's disease (HD) and aggressive non-Hodgkin's lymphomas (NHL) are considered chemotherapy–responsive tumors, many patients either relapse or never achieve remission.[1,2] The prognosis of these patients is generally poor with conventional chemo-radiotherapy salvage regimens.[3,4] However, high-dose chemotherapy followed by stem cell rescue was shown to improve disease-free survival when compared with salvage chemotherapy alone in chemosensitive relapsed patients.[5] Effective second line therapies are thus required to reduce tumor burden prior to autologous stem cell transplantation (ASCT). Several studies have indicated that ifosfamide-based regimens can induce significant clinical responses in refractory or relapsed lymphoma patients prior to ASCT and, at the same time, efficiently mobilize transplantable hematopoietic stem/progenitor cells (PBSC) in a substantial proportion of patients.[6-9]

Filgrastim (recombinant methionyl human granulocyte colony-stimulating factor [G-CSF]) is a recombinant growth factor widely used in cancer patients to accelerate neutrophil recovery after chemotherapy and to mobilize CD34+ cells into peripheral blood (PB).[10] Filgrastim has a half-life of 3-4 hours and is conventionally administered as daily subcutaneous (s.c.) injections.[11] Pegfilgrastim is a pegylated form of filgrastim with a prolonged terminal elimination half-life of 33 hours, high serum concentrations and self-regulating serum levels as a function of neutrophil count.[12,13] Early studies have shown that pegfilgrastim stimulates granulocytopoiesis in steady-state and neutropenic mice as efficiently as filgras-

tim.[13,14] More recently, several phase II and randomized phase III trials have demonstrated that a single fixed dose (6 mg) of pegfilgrastim is as safe and well tolerated as standard daily filgrastim administrations and provides similar neutrophil support after chemotherapy in cancer patients.[15-21] In addition, the longer half-life of this form of pegfilgrastim allows better scheduling and facilitates compliance because of the reduced number of injections, and may thus improve the management of neutropenia. Preliminary data on mice and human normal volunteers have also suggested that pegfilgrastim may be able to mobilize PBSC in a more timely fashion than filgrastim, with the additional advantage of only a single dose administration being necessary instead of daily s.c. injections.[14] Few data have been reported on the use of pegfilgrastim for mobilizing PBSC in cancer patients.[16,22,23] In a phase I study on thirteen patients with non-small-cell lung cancer, the effects of pegfilgrastim on the absolute neutrophil count (ANC) and mobilization of $CD34^+$ cells were comparable or slightly better than those observed with filgrastim.[16] However, the limited number of patients studied and the lack of stem cell collection and subsequent reinfusion data made it difficult to draw any conclusion. Of note, only preliminary results are currently available on the ability of pegfilgrastim to mobilize PBSC in patients with hematologic malignancies.[22,23]

In this phase II study, we investigated whether a single 6 mg dose of pegfilgrastim administered after chemotherapy is able to mobilize $CD34^+$ stem cells efficiently into the PB of patients with pretreated HD and aggressive NHL eligible for ASCT.

Table 1. Patients' characteristics.

Disease	
Hodgkin's disease	4
NHL DLBC	8
NHL FL grade III	9
NHL MCL	3
NHL T-cell	1
Sex	
Male	11
Female	14
Median age (range)	49 (26-66)
Median body weight (range)	70 (48-109)
Disease stage	
II	8
III	5
IV	12
IPI score (NHL only)	
0	9
1	10
≥2	2
Bulky disease	
Yes	10
No	15
Disease status	
Partial response	14
Refractory	2
Relapsed	9
Prior lines of chemotherapy (median) (range)	1 (1-4)
Prior radiotherapy (%)	5/25 (20%)

HD, Hodgkin's disease; NHL, non-Hodgkin's lymphoma; DLBC: diffuse large B cell lymphoma; MCL, mantle cell lymphoma; FL grade III: grade III follicular lymphoma.

Design and Methods

Patients

Twenty-five consecutive pretreated adult patients with HD or aggressive NHL were studied between September 2003 and March 2004. Patients were enrolled in the study if they had experienced treatment failure with at least one prior chemotherapy regimen and were eligible for stem cell mobilization and ASCT according to our institutional protocols. In particular, all patients were required to have a confirmed histologic diagnosis of aggressive NHL or HD according to the REAL classification,[24] disease stage II to IV according to the Ann Arbor staging system[25] and an Eastern Cooperative Oncology Group (ECOG) performance status ≤2. Exclusion criteria were: major organ dysfunction, myelosuppressive chemotherapy within the last 4 weeks, administration of any hematopoietic cytokine within 2 weeks before mobilization and pelvic irradiation before stem cell collection. Patients with a positive test for human immunodeficiency virus (HIV) or any form of active hepatitis were also excluded, as were pregnant or nursing females. Low baseline ANC and platelet count were not routine exclusion criteria. The patients' diagnosis, sex, median age, weight, median number of prior chemotherapies, International Prognostic Index (IPI) score and disease status at the time of mobilization, as well as the proportion that had received prior radiotherapy, are listed in Table 1. All subjects gave written informed consent to inclusion in the study. The protocol was approved by the Institutional Ethics Committee.

Chemotherapy and mobilizing treatment

The salvage chemotherapy regimen (IEV) was as follows:[8,9] ifosfamide 2500 mg/m^2/day intravenously (i.v.) over 4 hours followed by mesna (3 g/m^2) and hydration over 10 h daily to protect against urothelial toxicity (days 1 to 3); epirubicin 100 mg/m^2 i.v. (day 1); etoposide 150 mg/m^2 i.v. (days 1 to 3). Chemotherapy

was given in an outpatient setting. A fixed dose of 6 mg of pegfilgrastim (Neulasta; Amgen Inc., Thousand Oaks, CA, USA) supplied in single-use, preservative-free prefilled syringes, was administered as single s.c. injection on day 6, three days after the end of the chemotherapy regimen.

Leukaphereses and PBSC processing

Stem cell collection was started when the absolute number of circulating CD34+ cells was >10×10^6/L[27-29] during the recovery phase from IEV chemotherapy. As already reported,[26-28] PBSC were collected by using either a Fenwal CS3000 continuous flow blood cell separator (Baxter, Rome, Italy) with the modified procedure N.1 program or a Cobe Spectra separator (Cobe BCT Inc., Lakewood, Colorado, USA). Standard volume leukaphereses were performed daily until the collection of a target cell dose of 2×10^6 CD34+ cells/kg was achieved. The minimum number of stem cells to proceed to transplant was 1×10^6 CD34+ cells/kg. The CD34+ cell count was determined by flow cytometry as previously reported.[26-28] In brief, cells were incubated at 4°C for 30 minutes with the anti-CD34 phycoerythrin-conjugated monoclonal antibody HPCA2 or an irrelevant isotype matched control antibody (Becton Dickinson, Milan Italy). Immunofluorescence analysis was performed using FACScan equipment (Becton Dickinson). A minimum of 10,000 events were collected in list mode on FACScan software. The apheresis products were concentrated and frozen in 10% dimethyl sulfoxide using controlled-rate liquid nitrogen freezing.[28] At the time of reinfusion, PBSC were rapidly thawed to 37°C and reinfused via a central line.[28]

Conditioning regimen, supportive care and clinical monitoring

All patients were conditioned with BEAM chemotherapy (carmustine, 300 mg/m^2 i.v. on day –7; cytarabine, 200 mg/m^2 i.v. twice daily from day -6 to -3; etoposide, 200 mg/m^2 i.v. from day -6 to -3; melphalan, 140 mg/m^2 on day -2)[29] before reinfusion of autologous stem cells. All patients received 5 μg/kg/day of filgrastim (Amgen) starting on day +6 after the autograft. Patients were nursed in single or double rooms in reverse isolation and received antimicrobial prophylaxis that consisted of oral nystatin and ciprofloxacin. Packed red blood cells and platelet transfusions were administered to maintain a hemoglobin level greater than 8 g/dL and a platelet count greater than 10×10^9/L. Patients were treated with broad-spectrum antibiotics when fever developed and the ANC was less than 0.5×10^9/L. Amphotericin B (1 mg/kg/day) was added if patients had persistent fever after 4-7 days of intravenous antimicrobial therapy. Patients underwent daily assessment of symptoms and physical examination during hospitalization and weekly after discharge. As previously reported,[29] laboratory work-up was performed before the transplant, daily during the hospital admission and weekly after discharge.

Hematopoietic recovery and clinical end-points

The primary end-point of the study was the successful mobilization of a target cell dose of 2×10^6 CD34+ cells/kg of the patient's actual body weight (minimum 1×10^6 CD34+ cells/kg) after IEV chemotherapy in patients with relapsed/refractory HD or aggressive NHL. Secondary end-points were: number of leukaphereses required to obtain the target CD34+ cell dose, assessment of the kinetics of CD34+ cell mobilization, tolerability of pegfilgrastim treatment, duration of severe (grade III-IV WHO) neutropenia, incidence of febrile neutropenic episodes and documented infections, and use of intravenous antibiotics. We also evaluated the engraftment capacity of pegfilgrastim-mobilized CD34+ cells after the BEAM myeloablative conditioning regimen.

Statistical analysis

This was a phase II study. The necessary sample was calculated using Fleming's single stage procedure. According to available data on IEV chemotherapy and filgrastim, successful mobilization of PBSC (defined as the collection of ≥2×10^6 CD34+ cells/kg) had been achieved in 74% of a similar cohort of patients.[9] Thus, p_0 and p_1 were set at 0.5 and 0.8, with a two sided α=0.05 and 1-β= 90%; the number of patients required was calculated to be 25. The study treatment would be considered efficient if at least 18 out of 25 patients were successfully mobilized. All enrolled patients receiving at least one dose of pegfilgrastim were considered for analysis. The results are presented as median values and ranges. The probabilities of neutrophil and platelet recovery are presented according to the Kaplan-Meier method. The association between the number of CD34+ cells collected and the patients' body weight, and the association between the number of CD34+ cells infused and the time to hematopoietic recovery were assessed by Pearson's correlation test.

Results

Study patients

Between September 2003 and March 2004, 25 pretreated consecutive patients with HD (=4) or aggressive NHL (=21) were enrolled in this study. Table 1 reports the patients' demographics and some of the most important clinical parameters widely consid-

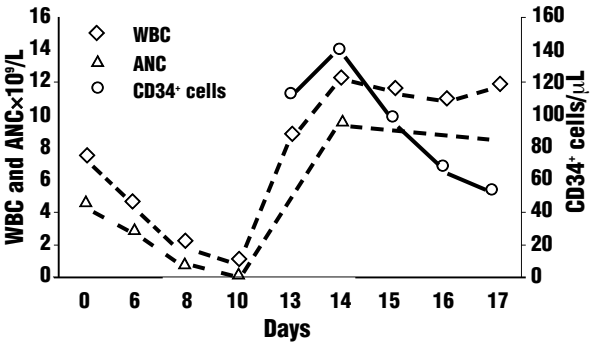

Figure 1. Median white blood cell count (WBC), absolute neutrophil count (ANC) and concentration of mobilized CD34⁺ stem cells in 25 lymphoma patients receiving salvage IEV chemotherapy and a single 6 mg pegfilgrastim injection.

Table 2. Engraftment data of pegfilgrastim-mobilized PBSC.

	Median	*Range*
Days to ANC> 0.5×10⁹/L	10	9-16
Days to PLT> 20×10⁹/L	11	9-13
Days to PLT> 50×10⁹/L	14	12-18
% Documented Infections	20	
Parenteral antibiotics		
Patients (%)	60	
Days	4	0-8
Days on G-CSF after ASCT*	6	4-10
Days to hospital discharge	12	9-18

*ANC: absolute neutrophil count; PLT, platelet count. *All patients received 5 μg/kg/day of filgrastim starting on day +6 after the autograft.*

ered to affect BM function and stem cell mobilization such as the amount of previous chemotherapy and radiotherapy. Sixteen patients were eligible for salvage chemotherapy and ASCT as they had not achieved complete remission with first line chemotherapy: 14 showed a partial response (i.e. more than 50% tumor mass reduction) and 2 were considered to be primary refractory (i.e. less than 50% response). Nine additional patients had received multiple lines of chemotherapy before stem cell mobilization. Five of the 25 patients (20%) had been previously irradiated.

IEV chemotherapy and CD34⁺ cell mobilization

Following salvage chemotherapy, all patients had grade 4 neutropenia that lasted a median of 1.5 days.[1-3] No episodes of febrile neutropenia were recorded and none of the patients received intravenous antibiotics. Pegfilgrastim treatment was well tolerated and only 2/25 patients required medication for bone pain. CD34⁺ cells were mobilized in all patients (i.e. the peak value was always greater than 10×10⁶/L). The median peak value of circulating CD34⁺ cells after IEV chemotherapy and pegfilgrastim was 141×10⁶/L (range 12.8-386) and occurred in 19/25 patients on day +14 (range, 13-16). Twenty-three of the 25 patients underwent a single standard volume apheresis to collect a median of 8.7 CD34⁺ cells/kg (1.78-17.3). Twenty-four of the 25 patients (96%) reached the target cell dose of 2×10⁶ CD34⁺ cells/kg. When we analyzed the kinetics of PBSC mobilization (Figure 1), we found that all patients had a high concentration of PB CD34⁺ cells (>50×10⁶/L) for several days after the achievement of the peak value. No differences were noted according to the patients' diagnosis, previous treatment or body weight (*data not shown*).

Engraftment results

Engraftment data of pegfilgrastim-mobilized CD34⁺ cells in 25 patients transplanted after high dose chemotherapy are shown in Table 2 and Figure 2. The only patient who mobilized slightly less than the target CD34⁺ cell dose (1.78×10⁶/kg) is also included in this series. At a median of 42 days from PBSC collection (range 26-85), lymphoma patients were reinfused with a median of 4.2×10⁶ CD34⁺ cells/kg (range 1.76-7.9) (Table 2). Of note, according to our institutional policy when the total number of CD34⁺ cells collected is greater than 5×10⁶/kg, PBSC are split into two aliquots and only one aliquot (>2.5×10⁶/kg) is reinfused. The second aliquot is kept cryopreserved to perform a second ASCT in the case of subsequent relapse of the disease. The median time to neutrophil engraftment after ASCT was 10 days. In line with the fast neutrophil recovery, the percentage of lymphoma patients with documented infections was low. The median times to unsupported platelet counts of 20 and 50×10⁹/L were 11 and 14 days, respectively. No significant correlation was found between the number of CD34⁺ cells reinfused and time to neutrophil and platelet engraftment in this population of patients who were all reinfused with high numbers of PBPC. The median time of hospitalization after autograft was 12 days. No patients were readmitted into hospital after discharge because of late infections.

Discussion

Autologous PBSC are extensively used to provide rapid and sustained hematopoietic recovery after myeloablative treatment in patients with hematolog-

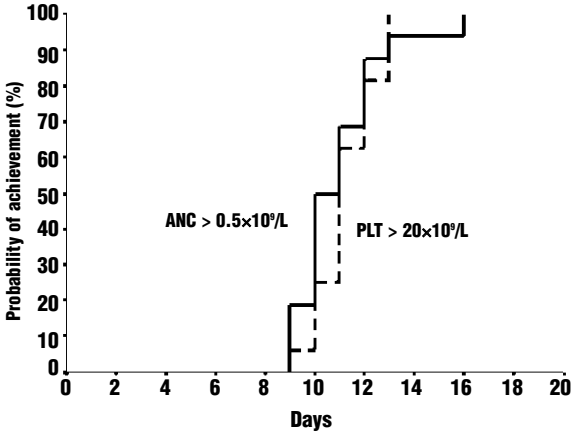

Figure 2. Kaplan-Meier plot of probability of recovery of the absolute neutrophil count (ANC) to 0.5×10⁹/L and recovery to an unsupported platelet (PLT) count of 20×10⁹/L after myeloablative chemotherapy and reinfusion of pegfilgrastim-mobilized PBSC.

ic malignancies. Because of the less invasive collection methods, faster neutrophil and platelet engraftment, earlier hospital discharge and lower overall cost, PB has, in fact, largely replaced BM as the source of transplantable stem cells.[30,31] Administration of G-CSF, alone or in combination with chemotherapy, is widely considered the most effective method of increasing the number of circulating CD34+ stem cells.[30] The number of CD34+ cells infused correlates with the rate of hematopoietic reconstitution. Thus, patients receiving at least 2×10⁶ CD34+ cells/kg show a rapid neutrophil recovery, and patients transplanted with ≥5×10⁶ CD34+ cells/kg have faster multilineage engraftment. Conversely, below the minimum threshold level of 1×10⁶ CD34+ cells/kg reinfused, the risk of delayed hematopoietic recovery and increased transplantation mortality is high.[32] In addition, a significant proportion of cancer patients (10 to 30%), either mobilize stem cells into the PB poorly or do not mobilize them with current approaches; this inadequate mobilization depends on underlying disease, previous chemoradiotherapy, the interval between last therapy and mobilization, marrow fibrosis and the number of premobilization circulating stem cells.[33-36] In our experience, 26% of patients with resistant/relapsed HD and aggressive NHL undergoing mobilization with IEV chemotherapy and filgrastim did not yield the target cell dose of 2×10⁶ CD34+ cells/kg.[9] Taking into consideration that ASCT has proven to be the best therapeutic option for such patients,[5,37] the development of novel strategies for efficient and safe mobilization of PBSC are warranted in order to be able to offer transplantation to as many patients as possible. In this context we recently demonstrated that G-CSF-primed BM represents an effective source of stem cells for cancer patients who are eligible for ASCT but who mobilize poorly.[28] Recently, various phase II and randomized phase III studies have shown that a single fixed dose of 6 mg pegfilgrastim is as effective as multiple injections of standard filgrastim in supporting neutrophil recovery after chemotherapy in patients with malignancies.[15-21] In addition, data published in abstract form suggest that pegfilgrastim, at doses ranging from 6 to 12 mg, is capable of mobilizing PBSC that may be collected and transplanted in patients with multiple myeloma and lymphomas.[22,23] Notably, in an animal model, pegfilgrastim proved to be markedly superior to standard filgrastim for the prevention of graft-versus-host disease following allogeneic stem cell transplantation, due to the generation of interleukin-10-producing regulatory T cells.[38] In this study we investigated whether a single 6 mg dose of pegfilgrastim administered after chemotherapy is capable of mobilizing CD34+ stem cells efficiently into the PB of patients with previously treated HD and aggressive NHL eligible for ASCT.

Our results confirmed that, like daily filgrastim, pegfilgrastim is well tolerated and not associated with significant toxicity.[39] Only 2 patients (8%) suffered bone pain requiring treatment with paracetamol. In addition, for the first time, we demonstrated that pegfilgrastim as an adjunct to chemotherapy is a predictable and highly effective mobilization regimen in lymphoma patients. In fact, all but one of the patients treated (96%) showed successful mobilization, defined as the collection of a target dose of 2×10⁶ CD34+ cells/kg. Twenty-three of the 25 patients (92%) underwent a single standard volume leukapheresis. The only patient who failed to achieve the target cell dose was nevertheless successfully transplanted with 1.78×10⁶ CD34+ cells/kg. These data look promising when compared with those previously recorded in a series of pretreated lymphoma patients receiving IEV salvage chemotherapy and daily filgrastim administration.[9] However, it should be noted that in the current study only 9 of 25 patients (36%) had received more than one line of chemotherapy prior to salvage chemotherapy and mobilization, while 33 of the 62 patients (53.2%) reported earlier[9] had been heavily pretreated. This finding may partly explain the difference in the percentage of successful procedures (96% vs 74%). Thus, in the absence of a randomized trial we cannot draw any firm conclusion on the superiority of pegfilgrastim as opposed to filgrastim.

Of note, the efficacy of pegfilgrastim as a mobilizing agent was independent of the patient's actual body weight, showing that a fixed dose of 6 mg is effective across a broad range of body weights (48-109 kg in this study). Furthermore, no difference in PBSC collection was observed between patients

weighing more or less than 70 kg (ie, the median weight of our patient population). In current PBSC mobilization practice, many groups use weight-based dosing of filgrastim, and administer twice the dose usually employed for the prevention of febrile neutropenia after chemotherapy. Similarly, in some preliminary mobilization studies of pegfilgrastim,[16,22,23] a single 12 mg dose was given. However, our data suggest that a lower dose of pegfilgrastim (i.e. 6 mg) is highly effective at mobilizing CD34+ cells and probably more cost-effective.

In this view, our previous experience with lymphoma patients receiving IEV salvage chemotherapy and 5 μg/kg of daily filgrastim administration,[9] demonstrated that a median number of 9 vials of the drug was required for PBSC collection. The average price of one vial of filgrastim in Europe is 115 Euros (range: 60-196; source Amgen Italia), whereas the price of pegfilgrastim is 930 Euros (range 900-1000; source Amgen Italia). Thus, the cost of a single injection of 6 mg of pegfilgrastim is roughly equivalent to 8-9 days of treatment with filgrastim used at the dosage of 5 μg/kg for patients with a body weight lower than 80 kg and 4-5 days when the dose of filgrastim is 10 μg/kg. In addition, it should be noted that pegfilgrastim allowed the collection of the target dose of CD34+ cells almost invariably with a single leukapheresis, whereas 13/33 (39%) patients required two aphereses in our previous experience with daily filgrastim injections.[9]

When the kinetics of PBSC mobilization were analyzed, we found that the number of circulating CD34+ cells declined slowly after the peak value had been achieved and the median concentration of PBSC was > 50 cells×10^6/L for at least five additional days. At the same time, WBC and ANC remained stable. In contrast, when we used filgrastim after the IEV regimen we observed a rapid clearance of PB CD34+ cells after the peak value (which occurred on day +14, as it did with pegfilgrastim) and this finding was associated with the constant increase of WBC and ANC (*data not shown*). The long-term persistence of CD34+ cells in PB may be due to the prolonged half-life of pegfilgrastim (i.e. 33 hours) and its reduced serum clearance as a function of neutrophil count.

Taken together, these data suggest that the timing of stem cell collection can be safely delayed if clinical problems emerge during the recovery phase from neutropenia (e.g. infections or thrombocytopenia) or if the PBSC peak value occurs during the weekend. More importantly, the extended mobilization time induced by pegfilgrastim may translate into a greater number of CD34+ cells collected. Finally, we showed that pegfilgrastim-mobilized CD34+ cells induced rapid and sustained multilineage hematopoietic recovery after myeloablative chemotherapy. In conclusion, a single 6 mg injection of pegfilgrastim was safe and well tolerated and resulted in efficient mobilization of CD34+ cells in lymphoma patients treated with IEV as salvage chemotherapy. Moreover, pegfilgrastim-mobilized CD34+ cells induced rapid engraftment when reinfused after high-dose chemotherapy. This study sets the stage for further trials designed to compare the efficacy of pegfilgrastim with that of filgrastim in patients who mobilize PBSC poorly.

MT, AC, PLZ and LA were primarily resposible for patient care in the outpatient department. AI and FB analyzed the data. MRM, SR, VG, OF, MR and RC were involved in stem cell harvesting and processing and data collection. MB gave the final approval before manuscript submission. RML designed the study, analyzed the data with AI and FB and wrote the manuscript with AI. The authors declare that they have no potential conflicts of interest. This research was supported by the University of Bologna (Funds for selected topics).

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