

ORIGINAL ARTICLE

Efficacy of single dose pegfilgrastim in enhancing the mobilization of CD34+ peripheral blood stem cells in aggressive lymphoma patients treated with cisplatin-aracytin-containing regimens

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Systematic data on the ability of pegfilgrastim to mobilize stem cells after chemotherapy are scarce. We evaluated the efficacy of a single 6 mg dose of pegfilgrastim for mobilizing peripheral blood stem cells (PBSC) in aggressive lymphoma patients. Between July 2004 and October 2005, 17 aggressive non-Hodgkin's lymphoma and 11 poor-risk Hodgkin's lymphoma were treated with cycles containing cisplatin-aracytin. At the end of chemotherapy, the patients received 6 mg of pegfilgrastim. Duration of grade 4 neutropenia, adverse events, time to neutrophil recovery, peak and harvest of CD34+ cells were recorded. Twenty-seven out of 28 patients harvested a median of 17.3×10^6 /CD34+ cells (range 2.5–28.9) after a median of 9 days (range 8–12 days), with a single apheresis procedure in 25 cases. All patients had grade 3–4 neutropenia, median duration 3 days. The only adverse event was mild bone pain. To date, 13 patients have been autografted with a median of 15.4×10^6 CD34+ pegfilgrastim-mobilized cells per kg (range 2.5–28.9) with rapid and sustained engraftment. Mobilization, harvesting and autografting of pegfilgrastim-mobilized PBC can be successfully achieved in pretreated patients with aggressive lymphoma.

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Introduction

Recently, a polyethylene glycol (PEG)-conjugated form of granulocyte colony-stimulating factor (G-CSF) has been introduced. In this formulation, filgrastim is bound covalently to a 20 kDa PEG molecule, which increases

the serum half-life of G-CSF owing to decreased renal elimination. As a result, therapeutic serum levels of G-CSF are maintained over a period of about 2 weeks following a subcutaneous injection of 6 mg single dose of pegfilgrastim.^{1,2} Some randomized studies have shown that in lymphoma patients, a single dose of pegfilgrastim per chemotherapy cycle provided neutrophil support with safety and efficacy similar to that observed with daily injections.^{3,4} In the last few years, the use of high-dose chemotherapy and autologous stem-cell transplantation (ASCT) has determined, in chemotherapy-responsive lymphoma patients, improved disease-free survival compared with salvage chemotherapy alone.⁵ Obviously, collection of sufficient numbers of peripheral blood stem cells (PBSC) is essential for safe transplant procedures. Current regimens for stem cell mobilization are based on subcutaneous injections of human recombinant G-CSF starting shortly after chemotherapy. Systematic data on the ability of pegfilgrastim to mobilize stem cells after chemotherapy are scarce.^{6–8}

In this study, we evaluated the efficacy of a single fixed 6 mg dose of pegfilgrastim after cisplatin-ARA-C-containing regimens in mobilizing PBSC in aggressive lymphoma patients. Furthermore, the possibility of a sufficient collection of CD34+ PBSC (cell dose $>2 \times 10^6$ /kg) in a single procedure was tested.

Patients and methods

Between July 2004 and October 2005, 28 patients with aggressive lymphoma (11 Hodgkin's lymphoma, 14 diffuse large B-cell and three anaplastic non-Hodgkin's lymphoma) were enrolled in this study. The patients were evaluated for disease localizations according to the Ann Arbor staging system, for risk assessment with International Prognostic Index (IPI) score and for disease status at the time of mobilization. The patients with major organ dysfunction, performance status more than 2, use of colony-stimulating factors within the last 3 weeks before mobilization, positive test for HIV or any form of active hepatitis were excluded. All patients had previously

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received one or more chemotherapy lines. All subjects gave written consent for inclusion in the study. The characteristics of patients are shown in Table 1.

The following chemotherapy cycles containing cisplatin were administered: DHAP (cisplatin 100 mg/m² 24-h continuous infusion day 1, cytarabine 2 g/m² every 12 h day 2, dexamethasone 20 mg intravenous (i.v.) × 4 days) or idarubicin, platinum, aracytin, dexamethasone (IPAD) (idarubicin 12 mg/m² i.v. day 1, cisplatin 50 mg/m² continuous infusion days 1 and 2, cytarabine 2 g/m² every 12 h day 2, dexamethasone 20 mg i.v. × 4 days). The patients were treated the first day (day +1) or the second day (day +2) after the end of chemotherapy with 6 mg subcutaneous single dose of pegfilgrastim for enhancing neutrophil recovery and improving CD34+ mobilization. PBSCs were usually harvested after the first course of cisplatin-aracytin-containing regimens. The harvest was performed after the second course of chemotherapy, after the chemosensitivity to DHAP regimen had been verified, in only three patients with resistant disease. When the patients had gone through the nadir of the leucocytes (WBC), the CD34+ cells in the peripheral blood were measured as soon as the WBC count rose above 1 × 10⁹/l; the concentration of CD34+ cells was determined according to International Society of Hematotherapy and Graft Engineering guidelines.⁹

Stem cell collection was started when the absolute number of CD34+ was more than 20/μl during the

recovery from cisplatin-aracytin-containing regimens. Leukapheresis was performed daily to reach the optimal target number of PBSC (>5 × 10⁶ CD34+ cell/kg). A PBSC collection of less than 2 × 10⁶ CD34+ cell/kg, which is associated with a higher risk of delayed engraftment,¹⁰ was considered as collection failure.

Duration of grade 4 neutropenia, adverse events, time to neutrophil and CD34+ cell recovery were recorded.

Results

The results of CD34+ cell harvests are reported in Table 2. IPAD regimen was administered to only five patients and one of them did not collect. Following the administration of either DHAP or IPAD regimens, recovery of leukocytes of more than 1 × 10⁹/l was observed after a median of 8 days (range 7–11) from the stimulation with pegfilgrastim; the maximum number of CD34+ cells in peripheral blood was reached on day +9 (median, range +8 to +12). In 27 patients, the median peak of absolute CD34+ cell number in the peripheral blood was 171.2/μl (range 21.15–544.5/μl). Of 28 patients submitted to cisplatin-aracytin-containing regimens and following stimulation with pegfilgrastim, 27 patients (96%) harvested a median of 17.3 × 10⁶/CD34+ cells/kg body weight (range 2.5–28.9). The median time from the first day of stimulation with pegfilgrastim to the first day of leukapheresis was 9 days (range 8–10) for DHAP regimen and 10 days (range 9–12) for IPAD regimen. The one patient who was unable to mobilize PBSC had been previously submitted to three lines of chemotherapy and was 65 years old. Two heavily pre-treated patients needed two apheresis procedures to obtain more than 2 × 10⁶/kg cells; in the other 25/27 patients (92%), a single apheresis procedure was sufficient to reach the optimal scheduled target, obtaining a median of 20.6 × 10⁶ CD34+ /kg body weight (range 5.4–45.8) (Table 2).

Grade 3–4 neutropenia was present in all patients, with a median duration of 3 days (range 1–5) for DHAP regimen and 4.5 days (range 3–7) for IPAD regimen. Grade 2–3 thrombocytopenia was present in all patients, with a median duration of 5 days (range 3–7). No patients had infectious episodes. The only adverse event induced by pegfilgrastim was mild bone pain.

At the time of writing, 13 patients have been autografted with a median of pegfilgrastim-mobilized cells of 15 × 10⁶ cells/kg (range 2.5–28.9) and all showed a rapid and sustained engraftment after high-dose chemotherapy.

Discussion

Filgrastim has been extensively used for more than 10 years to mobilize stem cells from hematologic patients, allowing adequate collection and transplantation of PBSCs.^{10,11} Adjunctive use of filgrastim also increases the speed and extent of neutrophil recovery after chemotherapy. However, filgrastim has a short serum half-life and must be given by daily injection. Pegfilgrastim was developed as a long-acting cytokine requiring only one dose per

Table 1 Patients' characteristics (N = 28) at study entry

Disease	No. of patients
Hodgkin's disease	11
DLBC NHL	14
T anaplastic NHL	1
B anaplastic NHL	2
Sex	
Male	18
Female	10
Median age (range)	43 (17–66)
Disease stage	
II	13
III	4
IV	11
IPI score (NHL only)	
1	1
2	10
>2	6
Bulky disease	
Yes	12
No	16
Disease status (at the time of harvest)	
Complete remission	8
Partial response	8
Refractory	9
Relapsed	3
Previous lines of chemotherapy (median) (range)	1 (1–3)
No. of patients with previous radiotherapy (%)	5/28 (17.8%)

Abbreviations: DLBC NHL = diffuse large B-cell non-Hodgkin's lymphoma; IPI = International Prognostic Index.

Table 2 Results of CD34+ cell harvest in all patients

Patient number	Age (years)	Disease	Disease status at harvest	Chemotherapy mobilizing regimen	Previous lines of chemotherapy	Neutropenia grade IV (days)	PBSC harvesting days from stimulation	No. of harvests	No. of CD34+ cell harvested ($n \times 10^6$ /kg)
1	67	B-NHL	Relapsed	IPAD	3	5	—	No harvest	—
2	54	HL	Second CR	DHAP	2 (+RT)	3	8	1	5.4
3	37	HL	PR	DHAP	1	3	10	1	20.3
4	47	B-NHL	PR	IPAD	1	7	10	1	20.9
5	60	B-NHL	PR	DHAP	2	4	10	2	5.7
6	30	B-NHL	PR	DHAP	1	3	8	1	14
7	58	T-NHL	CR	DHAP	1	1	9	1	7.5
8	52	HL	Refractory	DHAP	2	4	8	1	23.4
9	55	B-NHL	CR	DHAP	2	4	9	1	8.4
10	38	B-NHL	PR	DHAP	1	3	8	1	27
11	28	B-NHL	CR	IPAD	1	6	11	1	14.2
12	36	HL	Relapsed	DHAP	1	3	9	1	21.4
13	34	HL	PR	DHAP	1	2	9	1	7.6
14	45	B-NHL	PR	DHAP	2	4	10	2	3.4
15	44	B-NHL	CR	DHAP	1	5	10	1	14
16	49	HL	Refractory	DHAP	1 (+RT)	2	8	1	5.2
17	24	B-NHL	Second CR	DHAP	1	3	8	1	45.8
18	25	HL	PR	DHAP	1 (+RT)	4	8	1	12
19	32	HL	Refractory	DHAP	1	2	10	1	15.4
20	66	B-NHL	Refractory	IPAD	1	4	12	1	2.5
21	42	B-NHL	Refractory	IPAD	1	3	9	1	24.5
22	25	B-NHL	Refractory	DHAP	1	4	9	1	28.9
23	46	B-NHL	Refractory	DHAP	1	4	9	1	17.3
24	17	HL	Refractory	DHAP	1 (+RT)	3	9	1	16
25	28	HL	Relapsed	DHAP	3 (+RT)	1	9	1	8.6
26	54	B-NHL	CR	DHAP	1	1	8	1	8.64
27	19	B-NHL	CR	DHAP	1	2	10	1	31
28	42	HL	Refractory	DHAP	1	3	10	1	21.1

Abbreviations: B-NHL = non-Hodgkin's B-cell lymphoma; CR = complete remission; PR = partial remission; RT = radiotherapy; T-NHL = non-Hodgkin's T-cell lymphoma; HL = Hodgkin's lymphoma.

chemotherapy cycle, with safety and efficacy comparable to daily injections of filgrastim.² The fact that the 6 mg fixed dose does not compromise efficacy in patients weighing over 80 kg or tolerability in those weighing less than 60 kg¹² further simplifies the use of pegfilgrastim. In hematologic patients, the fixed 6 mg dose seems to provide support of neutrophils after chemotherapy¹³ and also in our patients post-chemotherapy neutropenia was short, 3–4 days median, without febrile episodes.

The optimal dose of pegfilgrastim for mobilizing PBSC is still unknown. Despite the fact that in healthy volunteers 12 mg dosage of pegfilgrastim seemed to determine a higher peak of CD34+ cells,¹⁴ in our experience this peak was high enough to allow an effective collection also with 6 mg dosage. The problem of optimal dosage could be particularly important for heavily pre-treated patients, who are usually less able to mobilize PBSC, often requiring a higher dosage. In our experience, the collection with 6 mg single dose was feasible and effective also in patients treated with more than one line of chemotherapy, including two patients treated with three lines. In fact, not only was it possible in the majority of patients (96%) to collect a high number (17.3×10^6 CD34+ cells/kg, median) of PBSC, reaching the optimal scheduled number of CD34+ of more than 5×10^6 /kg, but also to harvest this target dose with a single leukapheresis in 92% of them, probably reducing costs. The collected CD34+ cell dose, which was high in the majority of our patients, has an important impact on the outcome of salvage treatment

owing to the correlation between the number of CD34+ infused and the speed and durability of engraftment.¹⁵ These results are very similar to those recently published by Isidori *et al.*,⁷ who obtained effective mobilizations with the same 6 mg dosage of pegfilgrastim in lymphoma patients treated with ifosfamide, epirubicin, etoposide (IEV) salvage regimen. Moreover, the time of harvest seems predictable, because CD34+ increased rapidly from day 7 to day 12 from the stimulation, maintaining adequate levels for 2–4 days.¹⁴ Finally, similar good results were also described in 40 patients (16 with lymphoma) by Kroshinsky *et al.*,¹⁶ who obtained, in 72.5% of patients who underwent salvage chemotherapy, more than 4×10^6 CD34+ cells/kg after stimulation with 6 mg pegfilgrastim.

Some experiences with this drug were recently reported also in multiple myeloma patients. Steidl *et al.*⁶ compared 12 mg dosage of pegfilgrastim with daily administration of G-CSF, showing that this dose of pegfilgrastim was useful to shorten neutropenia after conventional mobilizing chemotherapy (namely cyclophosphamide 4g/m²). However, despite the increased dose of pegfilgrastim (12 mg), the collections were lower compared to the results observed in lymphoma patients, probably because the harvest is usually scheduled with different indications and in different phases of the disease. In fact, a partial clearance of plasma cells from bone marrow, without their complete disappearance is sufficient in myeloma patients to schedule the harvest after chemotherapy. Instead, in lymphoma patients

harvests are usually scheduled only when bone marrow shows no infiltration by lymphoma.

In myeloma patients, similar results were obtained using single doses of 6 mg pegfilgrastim, 12 mg pegfilgrastim and daily filgrastim, respectively, after the same chemotherapy (cyclophosphamide 4 g/m²).⁸ The two pegfilgrastim groups had earlier leukocyte recovery and harvested a number of CD34+ cells comparable to the filgrastim group (7.4 versus 10.8 × 10⁶ cells/kg). The following autograftings showed a similar reconstitution of leukocytes and platelets without differences in the two administered dosages of pegfilgrastim.

Sustained multilineage hematopoietic recovery after myeloablative chemotherapy was reported in all lymphoma transplanted with pegfilgrastim mobilized CD34+ cells.⁷ Also in our 13 patients who underwent ASCT, there was early engraftment and sustained hematological reconstitution.

In conclusion, in aggressive lymphoma patients a 6 mg single dose of pegfilgrastim after cisplatin-aracytin-containing regimens was effective and capable of mobilizing a high number of CD34+ cells. This result was obtained with a single collection in the majority of patients (86%), with increased convenience and improved compliance when compared to daily administration of G-CSF. Although in our transplanted lymphoma patients the pegfilgrastim-mobilized CD34+ cells induced rapid engraftment, further studies are needed to address optimal dose and schedule of pegfilgrastim administration in different hematological malignancies.

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