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Letter to the editor

Biosimilar G-CSF (filgrastim) is effective for peripheral blood stem cell mobilization and non-cryopreserved autologous transplantation

Efficacité d'un biosimilaire du filgrastim (G-CSF) au cours des autogreffes utilisant des cellules souches périphériques non cryopréservées

Peripheral blood stem cells (PBSCs) have become the most widely used source of hematopoietic progenitor cells for the support of high-dose chemotherapy and autologous stem cell transplantation (ASCT).

In autologous transplantation, G-CSF can be used alone for mobilizing CD34 stem cells, or after a chemotherapeutic mobilization regimen. Zarzio® (Sandoz Biopharmaceuticals, Paris, France) is a biosimilar G-CSF that was developed using Neupogen® as the reference product [1]. It is produced by recombinant DNA technology in bacteria (*E. coli*) from the full length human sequence for N-(L-Methionyl) G-CSF. Native G-CSF is a glycosylated protein but when produced in bacteria, a non-glycosylated protein is obtained; however, this is still biologically active. The composition of Zarzio® and Neupogen® is identical except for the buffer system, which is glutamate in Zarzio® and acetate for Neupogen® [2]. Zarzio® was approved in the EU in February 2009 for the same indications as Neupogen®. European guidelines recommend the use of biosimilar G-CSF for primary prophylaxis of chemotherapy-induced neutropenia, and biosimilar G-CSF was recently shown to be effective in this indication in an observational trial of 48 patients with solid tumors [3,4].

The objective of this study was to evaluate if biosimilar G-CSF has the same efficacy as originator G-CSF when used alone in the mobilization of PBSC for non-cryopreserved autologous PBSC transplantation.

A total of 20 patients with a hematological malignancy were included. Ten consecutive patients prospectively received biosimilar G-CSF (Zarzio®) in the period January to March 2012. These were compared with a retrospective control cohort ($n = 10$) who had been treated between 2009 and 2011 with originator G-CSF (Neupogen®).

The source of stem cells in all patients was mobilized autologous PBSCs. In both groups, patients received G-CSF at a dose of 15 μg/kg subcutaneously once daily for a minimum of 4 days. None of the patients had previously received chemotherapy for mobilization.

Leukapheresis was performed on days –2 and –1 using an Optia Spectra machine and CMN1 software with a default setting. The percentage of CD34+ cells was determined by an EPICS-XL (Beckmann Coulter) flow cytometer using Expo32 software; absolute CD34+ cell count was then calculated using ISHAGE double platform protocol. The products of the apheresis and 1-mL aliquots were kept in 10% ACD-A and stored in a conventional blood bank refrigerator at 4 °C, in their breathable collection bags. Failure of mobilization was defined as a count of less than 2×10^6/kg CD34+ cells/kg after two leukapheresis.

Stem cells were re-infused intravenously to the patient 24 hours after melphalan chemotherapy for patients with multiple myeloma (MM) and after CBV (cyclophosphamide, carmustine, etoposide), BEAM (carmustine, etoposide, standard dose, cytarabine, melphalan), or EAM (etoposide, high-dose cytarabine and melphalan) in patients with Hodgkin's lymphoma (HL).

Engraftment was calculated from day 0 of the SCT. Neutrophil engraftment required a sustained absolute neutrophil count of 500/μL. Engraftment of platelets required a platelet count of 20,000/μL (un-transfused), with no platelet transfusions within the preceding 48 hours.

There was no difference between the groups Zarzio® or Neupogen® when comparing patients characteristics (Table 1), results of apheresis (Table 2), side effects (Table 3) or engraftment (Table 4).

Our data are generally consistent with those from other centers who have reported experience with Zarzio®. In a study from Paris, France, 40 patients with a hematological malignancy scheduled to receive Zarzio® following first-cycle chemotherapy for treatment and autologous PBSC mobilization were prospectively included at a single center, and compared with a matched historical control group who had been treated with Neupogen® at the same center [5]. This study showed that median pre-leukapheresis peripheral blood WBC counts and CD34+ counts were similar in the Zarzio® and Neupogen® groups, as were the median number of CD34+ cells collected in the first leukapheresis and the number of leukapheresis necessary to harvest the minimum CD34+ cell count. In another study, Iannoto et al. reported that use of Zarzio® for PBSC ($n = 38$) was comparable with a historical cohort of patients with lymphoma or myeloma treated with originator G-CSF ($n = 50$). No significant differences were observed between groups with regard to PBSC stimulation or biological parameters of bone marrow recovery [6].

The optimal dose G-CSF in this setting is not well defined, and there are no data from randomized controlled trials assessing

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Table 1
Patient characteristics.

	Zarzio® ($n = 10$)	Neupogen® ($n = 10$)	P
Age (years) (median, range)	33.5 (17–64)	29 (22–61)	0.73
Sex			
Male (%)	8 (80%)	8 (80%)	1
Female (%)	2 (20%)	2 (20%)	1
Weight (kg) (median, range)	77.5 (40–98)	68.5 (43–115)	0.79
Disease			
Hodgkin lymphoma (%)	6 (60%)	6 (60%)	1
Multiple myeloma (%)	4 (40%)	4 (40%)	1
Previous lines of chemotherapy			
Single line (%)	8 (80%)	8 (80%)	1
Two lines (%)	2 (20%)	4 (20%)	1
Number of courses of previous chemotherapy (median, range)	7 (4–9)	6.5 (4–8)	0.58
Type of previous chemotherapy			
Multiple myeloma	VD × (4–6 courses)	VD × (4–6 courses)	–
Hodgkin lymphoma			
First line	ABVD × (4–8 courses)	ABVD × (4–8 courses)	–
Second line	DHAP or ICE × 3 courses	DHAP × 3 courses	–
Disease status at transplantation			
Complete remission (%)	8 (80%)	8 (80%)	1
Partial remission (%)	2 (20%)	2 (20%)	1
Intensification regime			
CBV (%)	0	5 (50%)	0.011
EAM (%)	6 (60%)	1 (10%)	0.02
Melphalan (%)	4 (40%)	4 (40%)	1

ABVD: doxorubicin-bleomycin-vimblastine-dacarbazine; VD: bortezomib-dexamethasone; DHAP: dexamethazone-cisplatin-cytarabine; ICE: ifosfamide-carboplatin-etoposide.

Table 2
Apheresis.

	Zarzio® ($n = 10$)	Neupogen® ($n = 10$)	P
Number of leukapheresis (median, range)	1 (1–3)	1 (1–2)	1
Total volume (mL) (median, range)			
1st apheresis	360 (200–520)	370 (220–420)	0.87
2nd apheresis	330 (200–400)	290 (280–300)	0.32
3rd apheresis	400[a]	0	–
White blood cell count (10^9/L) at day 1 of mobilization (median, range)	24.5×10^9/L (10.3–56.9)	24.75×10^9/L (16.7–36.8)	0.88
White blood cell count (10^9/L) at day 5 of mobilization (median, range)	35.5×10^9/L (26.6–65.4)	37.5×10^9/L (20.9–67.7)	0.96
Total of CD34+ cells/kg (10^6) (median, range)	4.10×10^6 (0.25–4.84)	2.71×10^6 (1.22–10.3)	0.86
Failure of mobilization	2	2	1

[a] The third apheresis was applied only in one patient.

Table 3
Side effect.

	Zarzio® ($n = 10$)	Neupogen® ($n = 10$)	P
Bone pain	3	2	0.6
Headache	3	1	0.27

Table 4
Engraftment.

	Zarzio® ($n = 10$)	Neupogen® ($n = 10$)	P
Leucocyte engraftment (day, median, range)	12 (10–16)	14 (10–17)	0.47
Platelet engraftment (day)	13 (8–15)	12 (10–23)	0.44
Growth factor use (day)	0	0	1

the effect of G-CSF dose on non-chemotherapy based mobilization regimens in autologous stem transplant. In our procedure, both Zarzio® and Neupogen® are used at the dose of 15 μg/kg per day, this dose is supported by previous data in allogeneic donors that suggests that high-dose G-CSF improve yields. In a randomized controlled trial, 50 patients randomized to receive 8 or 16 μg/kg per day G-CSF following standard mobilization chemotherapy, had improved CD34+ yield and decreased time of engraftment with G-CSF [7].

In addition to simplifying the autograft procedure by avoiding the need for cryopreservation, to avoid side effects of chemotherapy mobilization, and the need for hospitalization another way of potentially reducing the cost associated with these procedures is to use a biosimilar G-CSF such as Zarzio®. A recent study compared the cost-efficiency of Zarzio® and originator G-CSF (Neupogen®) for prophylaxis or treatment of febrile neutropenia across the European Union G5 countries, with the authors concluding that Zarzio® was cost-efficient relative to Neupogen®; the cost of treatment ranged from €95.46 (1 day) to €1336.46 (14 days) for Zarzio® compared with €128.16 (1 day) to €1794.30 (14 days) for Neupogen® [8].

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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