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BRIEF REPORT

Mobilization of Hematopoietic Stem Cells into Peripheral Blood for Autologous Transplantation Seems Less Efficacious in Poor Mobilizers with the Use of a Biosimilar of Filgrastim and Plerixafor: A Retrospective Comparative Analysis

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ABSTRACT

Introduction: Biosimilars of granulocyte colony-stimulating factors (G-CSF) have shown similar efficacy to originator filgrastim (Neupogen® [NEU]; Amgen Inc.) as prophylaxis in neutropenia and in the mobilization of stem cells in patients receiving combination chemotherapy with G-CSF.

Methods: This was a retrospective study in which the characteristics of stem cell mobilization treated with a G-CSF alone were compared in 216 patients and 56 donors. The two G-CSF compared were NEU and the biosimilar filgrastim Zarzio® (Sandoz GmbH) (referred to hereafter as BIO). Primary objectives were mobilization rate (minimum of 10×10^3/ml CD34+ on day 4 of treatment [day +4]) and use of the immunostimulant plerixafor (PLEX) in each group.

Results: The general characteristics of the patients receiving NEU (n = 138) and those receiving BIO (n = 78) did not differ significantly. PLEX was used in 24% of BIO patients and in 25.7% of NEU patients. The median CD34+ cell count on day +4 was significantly lower in BIO patients who needed PLEX than in those who did not (2.4 vs. 4.8 $\times 10^3$/ml; p = 0.002), as was the final CD34+ cell count (2.5 vs. 3.3 $\times 10^6$/kg; p 0.03). Mobilization failure rate was higher in the BIO group than in the NEU group (20 vs. 0%; p = 0.01). With respect to donors, more than one apheresis was needed in three BIO donors, one of them with PLEX. The use of BIO was the only risk factor for mobilization failure in patients who needed PLEX

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(hazard ratio 10.3; 95% confidence interval 1.3–77.8).
Conclusion: The study revealed that BIO had a lower efficacy for stem cell mobilization when the only treatment was G-CSF, especially in poor mobilizers needing PLEX.

Keywords: Biosimilars; Plerixafor; Stem cell mobilization

Key Summary Points

Biosimilars for filgrastim have become widely used in place of originator filgrastim (Neupogen®) following study results showing no significant differences in efficacy between both formulations.

No data have been published to date comparing the efficacy of biosimilar filgrastim with originator filgrastim for stem cell mobilization in the setting of mobilization with granulocyte colony-stimulating factors (G-CSF) only.

We have respectively reviewed a series of 216 consecutive patients and 56 donors, analyzed separately, who were treated with only a G-CSF and compared the biosimilar Zarzio® and originator Neupogen in terms of efficacy of mobilization rate.

Our results show that biosimilar Zarzio might be less efficacious than originator filgrastim when used with plerixafor in patients who are poor mobilizers.

INTRODUCTION

Biosimilars of the granulocyte colony-stimulating factor (G-CSF) filgrastim were approved by the European Medicines Agency (EMA) in 2008 and by the US Food and Drug Administration (FDA) in 2015 as substitutes for treating registered indications of the originator G-CSF, including the prevention and treatment of neutropenia and the mobilization of peripheral blood (PB) stem cells [1, 2]. The main advantage of biosimilars over the originator G-CSF is the reduction in final costs, up to 80%, without a theoretical loss of efficacy, while preserving the posology and administration route [3–5]. Nevertheless, there is still an ongoing debate on the quality, efficacy, and safety of biosimilar G-CSF. Initial phase I–II prospective clinical trials and more recently published phase III ones indicate that both the originator G-CSF and biosimilar G-CSF do demonstrate equivalence in terms of efficacy and safety profile when being used to reduce chemotherapy-induced neutropenia and infectious-related complications in patients with oncohematological malignancies [6–10].

Biosimilars have also been used as a mobilizing agent of hematopoietic stem cells (HSC) in PB in the setting of autologous stem cell transplantation (auto-hematocrit [HCT]), and studies have examined equivalence between biosimilars and the original filgrastim (Neupogen® [NEU]; Amgen Inc.) in patients and healthy donors [11–16]. Although comparative studies with a historical control of NEU did not show significant statistical differences with respect to peak CD34+ cells in PB on day 4 of treatment, the total number of CD34+ cells in the final apheresis product, and the median number of apheresis per patient, most of these studies were non-randomized and focused on chemotherapy-based mobilization strategies and not on mobilization with G-CSF alone [17–19].

Plerixafor (PLEX; Mozobil®), an antagonist of CXCR4 chemokine receptor, is indicated in combination with G-CSF to mobilize HSC into PB in patients with non-Hodgkin's lymphoma (NHL) or multiple myeloma (MM) (USA) and in patients with lymphoma or MM (EU) who are poor mobilizers (insufficient CD34+ cells after apheresis, or low PB CD34+ cell counts precluding apheresis) [20–23]. Two randomized, double-blind, multicenter trials demonstrated that PLEX used in combination with a G-CSF mobilized HSC more efficiently than placebo used with a G-CSF in adult patients with NHL or MM [24, 25].

Our institute, the Catalan Institute of Oncology (ICO), switched in May 2016 from

using the originator filgrastim NEU to using biosimilar filgrastim Zarzio® (Sandoz GmbH), not only as primary/secondary prophylaxis of chemotherapy-induced neutropenia but also as a mobilizing agent of HSC for patients with MM or lymphoma candidates for auto-HCT, as well as for healthy donors. We hypothesized the efficacy of G-CSF (NEU vs. Zarzio [hereafter referred to as BIO]) might be different for mobilization procedures in the setting of no prior chemotherapy and analyzed the results of a retrospective series of both patients and healthy donors in terms of PLEX use and collection results.

METHODS

Patients

The ICO is a comprehensive cancer center that acts as an umbrella organization for four different Clinical Hematology Departments each integrated in one of four different university hospitals. These four departments share the same general clinical procedures, pharmacy policies, blood bank, apheresis procedures, and HSC collection procedures, which are centralized in the Blood and Tissue Bank of Catalunya (BST).

The study included consecutive adult patients (age $\geq$ 18 years) with the underlying diagnosis of MM and lymphoma who were candidates for auto-HCT, and healthy adult donors (age $\geq$ 18 years), from December 2013 to November 2017. Only HSC mobilization procedures performed with G-CSF as single agent were included in the study.

The scientific proposal was reviewed and approved by the ethical committee of the institution (ICO-IDIBELL), and all procedures were in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. All participants included in the study provided written informed consent.

Procedure

The G-CSF dose was 10 μg/kg (for patients) and 5 μg/kg (for healthy donors, unless significant weight differences) twice daily, for 5 consecutive days. The minimum level of CD34+ cells in PB (monitored on day 4 of treatment [day +4]) to proceed to apheresis the next day was 10×10^3/ml. If the minimum level was not reached on day +4, G-CSF was continued together with a single dose of PLEX 0.24 mg/kg administered subcutaneously that evening, after the G-CSF injection. On day +5, if the circulating CD34+ cells target was not reached, a second dose of PLEX would be administered; failure of this second dose to achieve the circulating CD34+ cells target was interpreted as mobilization failure.

The apheresis procedure was generally performed through a central venous catheter in all patients, but peripheral veins were used in all previous healthy donors, with a Spectra Optia Apheresis System (Terumo Corporation, Tokyo, Japan). The number of blood volumes per patient to be processed followed standard recommendations [23].

Definitions: Primary and Secondary Objectives

A poor mobilizer was defined as a patient who was unable to reach the minimum number of $CD34^+$ cells to proceed to the collection procedure (10×10^3/ml). Mobilization failure was defined as the inability to collect at least 2×10^6 $CD34^+$ cells/kg body weight in the final product, regardless of the use of PLEX.

The primary objective of the study was the comparison of the mobilization efficacy of NEU versus BIO alone (not in combination with chemotherapy), defined as a minimum number of CD34+ cells in the PB on day +4 (10×10^3/ml) and/or the collection of at least 2×10^6 CD34+ cells/kg for patients and 4×10^6 CD34+ cells/kg for healthy donors at the end of the apheresis procedure. Secondary objectives of the study were the use of PLEX following the indications of the recently published Catalano-Balear consensus [26] in both groups of patients

as well as the analysis of independent prognostic factors predicting the use of PLEX and mobilization failure. Finally, a cost-effectiveness analysis was conducted.

Statistical Analysis

Descriptive statistics were used to summarize the clinical data. Qualitative data were compared using the Chi-square test. A non-parametric test (Mann–Whitney *U* test) was used to compare medians for quantitative data.

A cost-effectiveness analysis (CEA) quantifies the relationship between intervention/product costs and the consequences of this, evaluated as specific pre-defined units. The relative value is expressed as a ratio:total costs divided by total effectiveness and is called the median cost-effectiveness (MCE). In general, a procedure with a low MCE is more cost-effective (lower cost by unit of benefit produced), whereas a higher MCE shows less efficiency in comparison to the costs [27].

Patient costs were calculated taking into consideration the total number of doses of G-CSF received per patient, PLEX if required, and each apheresis procedure (≥ 1). If a second mobilization was needed (all cases with 1 dose of cyclophosphamide 1 g/m^2), the costs of this second mobilization procedure were also included (chemotherapy, G-CSF dose, and apheresis).

Both Pharmacy and BST Deparment reported corresponding prices as follows: NEU 300 mcg (€28,060; €93.5/mcg); NEU 480 mcg (€44,916); BIO Zarzio 300 mcg (€6396; €21.3/mcg), BIO 480 mcg (€10,233); PLEX single dose (24 mg; €5473). Chemotherapy for a second mobilization with cyclophosphamide 1 g/m^2 carried a cost of €5.37/g. Each apheresis procedure cost €1096.24.

Binary logistic regression was performed using SPSS v19 software (IBM Inc., Armonk, NY, USA). Variables included in multivariate analysis were sex, age, weight, basal disease, pre-mobilization status, prior treatment lines, and type of G-CSF.

RESULTS

Patients

A total of 216 patients diagnosed with lymphoma (n = 102, of whom 88 had NHL) or MM candidates to be consolidated with auto-HCT (n = 114), from December 2013 to November 2017, were included in the analysis. Of these patients, 138 received NEU and 78 received BIO. There was no statistically significant differences in the general characteristics of the two patient groups (Table 1).

A total of 53 patients received PLEX, with no significant difference in the number of patients between the BIO and NEU groups (25.7 vs. 24%, respectively; p = 0.7). Of these 53 patients, eight received PLEX outside of the established indication, with a CD34+ level $> 10 \times 10^6$/ml on day +4 (range 10.7–13.5 $\times 10^6$/ml) and were subsequently excluded from the final analysis, which was based on the remaining 45 patients (Table 2). The median number of CD34+ cells on day +4 was significantly lower in patients in the BIO group receiving PLEX (n =15) than in those in the NEU group receiving PLEX (n = 30) (2.4 [range 0.7–9.8] vs. 4.8 [0.7–9.8] $\times 10^3$/ml; p = 0.02), with a higher proportion of patients in the BIO group within the range $< 5 \times 10^3$/ml (80 vs. 56.7%; p = 0.1). Moreover, a significantly higher proportion of patients in the BIO group compared to the NEU group needed more than one dose of PLEX (26.7 vs. 3.3%; p = 0.02) and required more than one apheresis (28.6 vs. 16.7%), although this latter difference was not statistically significant. Regarding patients not needing PLEX (Table 3), it is noteworthy the median number of CD34+ cells on day +4 was also significantly lower for patients in the BIO group (23.7 vs. 33.4; p = 0.03).

Mobilization failure was seen in five patients in total (2.3%), all of whom were diagnosed with NHL: three patients were in the BIO group and two were in the NEU group (3.8 vs. 1.4%; p = 0.2). PLEX was unsuccessfully used in the three BIO patients. With respect to the 45 patients who received PLEX, mobilization failure occurred three patients in the BIO group versus no patient in the NEU group (20 vs. 0%;

Table 1 General characteristics of patients

Variables[a]	All patients (n = 216)	NEU[b] group (n = 138 patients)	BIO[c] group (n = 78 patients)	p
Age (years)	56 (19–72)	55 (19–68)	57 (20–72%)	ns
Sex				
Male	126 (58.3%)	78 (56.5%)	48 (61.5%)	ns
Female	90 (41.7%)	60 (43.5%)	30 (38.5%)	
Weight (kg)	73.5 (44–121)	73 (44–117)	75 (47–121)	ns
Underlying disease				
Lymphoma	102 (47.2%)	59 (42.8%)	42 (53.8%)	0.1
Multiple myeloma	114 (52.8%)	79 (57.2%)	36 (46.2%)	
Disease status at auto-HCT				
CR	123 (56.9%)	74 (53.6%)	49 (62.8%)	ns
PR	87 (40.3%)	60 (43.5%)	27 (34.6%)	
SD/active	6 (2.8%)	4 (2.9%)	2 (2.6%)	
Number of prior lines				
0–1	130 (60.2%)	88 (63.8%)	42 (54%)	ns
2	76 (35.2%)	45 (32.6%)	31 (39.7%)	
≥ 3	10 (4.6%)	5 (3.6%)	5 (6.3%)	
Peripheral blood counts prior to mobilization:				
Leucocytes ($\times 10^6$/ml)	5.6 (1–17.8)	5.5 (1–17.8)	5.6 (2.2–14.2)	ns
Platelets ($\times 10^6$/ml)	221 (57–525)	217 (57–525)	234 (85–423)	ns
Dose of G-CSF (μg)	1560 (600–2040)	1560 (600–1920)	1560 (600–2040)	ns
Price G-CSF (EUR/day)	112,240 (12,792–179,664)	145,952 (56,120–179,664)	33,258 (12,792–43,491))	< 0.01
Plerixafor	53 (24.5%)	33 (24%)	20 (25.6%)	ns
1 dose	47 (21.8%)	32 (23.2%)	15 (19.2%)	
2 doses	6 (2.8%)	1 (0.7%)	5 (6.4%)	0.05
Number of apheresis				
0	2 (0.9%)	1 (0.7%)	1 (1.3%)	ns
1	181 (83.3%)	113 (81.9%)	68 (87.2%)	
2	31 (14.4%)	23 (16.7%)	8 (10.3%)	
3	2 (0.9%)	1 (0.7%)	1 (1.3%)	
CD34+ cells on day +4 ($\times 10^3$/ml)	18.8 (0.7–185)	20.2 (0.7–185)	17.3 (0.7–152)	0.1

Table 1 continued

Variables[a]	All patients (n = 216)	NEU[b] group (n = 138 patients)	BIO[c] group (n = 78 patients)	p
$< 5 \times 10^3$/ml	30 (13.9%)	17 (12.3%)	13 (16.7%)	
5–10 $\times 10^3$/ml	25 (11.6%)	20 (14.5%)	5 (6.4%)	0.07
10–15 $\times 10^3$/ml	40 (18.5%)	20 (14.5%)	2 0(25.6%)	
$> 15 \times 10^3$/ml	121 (56%)	81 (58.7%)	40 (56%)	
CD34+ cells on day +5 ($\times 10^3$/ml)	34.2 (2.5–244)	34.6 (4.1–244)	29 (2.5–223)	ns
Total CD34 + cells collected ($\times 10^6$/kg)	4.3 (0.6–20.7)	4.3 (0.8–20.7)	4.13 (0.6–20.6)	ns
Mobilization failure (%)	5 (2.%)	2 (1.4%)	3 (3.8%)	ns
Auto-HCT yes/no	214 (99.1%)/ 2	137 (99.3%)	76 (97.4%)	ns

CR Complete remission, *day +4*, *+5* days 4, 5, respectively, of treatment, *G-CSF* granulocyte colony-stimulating factor, *HCT* hematocrit, NS not significant, *PR* partial remission, *SD* stable disease

[a] Variables in table are reported as the median with the range in parenthesis or as the number of patients with the percentage in parenthesis

[b] NEU refers to Neupogen® (Amgen Inc.), the originator filgrastim

[c] BIO refers to biosimilar filgrastim Zarzio® (Sandoz GmbH)

p = 0.01). A second mobilization attempt was indicated in one NEU patient (the other one progressed and auto-HCT was not subsequently indicated) and in two of the three patients in the BIO group, after prior cyclophosphamide (1 g/m^2). These two BIO patients once again needed PLEX and successfully mobilized after one apheresis procedure. Auto-HCT could be done in all but two cases (due to progression and failure mobilization, respectively).

Multivariable analysis (Table 4) showed three variables were independent risk factors for PLEX use: age, basal disease (lymphoma), and the number of pre-mobilization therapies. On the other hand, the use of BIO was the only risk factor associated to mobilization failure in patients receiving PLEX (hazard ratio 10.3, 95% confidence interval 1.3–77.8, p = 0.02).

Donors

A total of 56 related donors were mobilized during the study period, of whom 33 received NEU and 23 received BIO (Table 5). Donors receiving BIO were significantly younger than those receiving NEU and were predominantly females, but no differences were found in terms of mobilization outcomes (CD34+ cells on days +4 and +5). However, three donors receiving BIO needed more than one apheresis to achieve the minimum target, and one of these even needed PLEX.

Cost-Effectiveness Analysis in the Patients' Cohort

The cost-effectiveness analysis based on the CD34+ cell levels in PB on day +4 was favorable for BIO since the MCE was 4.41-fold lower for BIO than for NEU (193.7991 vs. 856.3112, respectively). With respect to the final number of CD34+ cells collected in the apheresis product, the analysis also favored BIO over NEU, with the MCE being 4.2-fold lower for BIO (152.4128 vs. 654.6695, respectively).

Table 2 General characteristics and mobilization data for patients who received plerixafor with CD34+ $< 10 \times 10^3$/ml on days +4 or +5

Variables[a]	All patients receiving PLEX (n = 45)	Patients in NEU group receiving PLEX (n = 30)	Patients in BIO group receiving PLEX (n = 15)	p
Age (years)	54 (20–68)	59 (20–68)	55 (20–67)	ns
Weight (kg)	75 (53–117)	77 (53–110)	74 (55–117)	ns
Sex				
Male	29 (64.4%)	19 (63.3%)	10 (66.7%)	ns
Female	16 (35.6%)	11 (36.7%)	5 (33.3%)	
Underlying disease				0.3
Lymphoma	15 (77.8%)	2 (73.3%)	13 (86.7%)	
Multiple myeloma	10 (22.2%)	8 (26.7%)	2 (13.3%)	
Disease status at auto-HCT				ns
CR	30 (66.7%)	21 (70%)	9 (60%)	
PR	14 (31.1%)	9 (30%)	5 (33.3%)	
SD/active	1 (2.2%)	0	1 (6.7%)	
Number of prior lines				ns
0–1	15 (33.3%)	12 (40%)	3 (20%)	
2	23 (51.1%)	14 (46.7%)	9 (60%)	
≥ 3	7 (15.6%)	4 (13.3%)	3 (20%)	
Peripheral counts prior to mobilization				ns
Leucocytes ($\times 10^6$/ml)	4.7 (1.8–9.3)	4.6 (1.8–9.3)	5.1 (2.2–8.4)	
Platelets ($\times 10^6$/ml)	181 (57–340)	183 (57–263)	182 (85–340)	
CD34+ cells on day +4 ($\times 10^3$/ml)	4.5 (0.7–9.8)	4.8 (0.7–9.8)	2.4 (0.7–9.8)	0.02
$< 5 \times 10^3$/ml	29 (64.4%)	17 (56.7%)	12 (80%)	0.1
5–10 $\times 10^3$/ml	16 (35.6%)	13 (43.3%)	3 (20%)	
CD34+ cells on day +5 ($\times 10^3$/ml)	22.1 (2.5–82.1)	20.7 (4.1–82.1)	13.8 (2.5–58.8)	0.08
Total number of mobilized CD34+ cells ($\times 10^6$/ kg)	3.7 (0.5–14.7)	3.3 (1.6–14.7)	2.5 (0.5–4.9)	0.03
More than 1 dose of PLEX	5 (11.1%)	1 (3.3%)	4 (26.7%)	0.02
> 1 Apheresis procedure	9 (20%)	5 (16.7%)	4 (28.6%)	ns

Table 2 continued

Variables[a]	All patients receiving PLEX (n = 45)	Patients in NEU group receiving PLEX (n = 30)	Patients in BIO group receiving PLEX (n = 15)	p
Mobilization failure	3 (6.7%)	0	3 (20%)	0.01

PLEX Plerixafor

[a] Variables in table are reported as the median with the range in parenthesis or as the number of patients with the percentage in parenthesis

DISCUSSION

The introduction of biosimilars into clinical practice is based on the finding of biological products being equivalent to originators in terms of efficacy and toxicity profile, with the same posology and administration and the advantage of a significant decrease in total costs [28]. In the study reported here, the originator filgrastim NEU is significantly more expensive than the biosimilar filgrastim Zarzio (here referred to as BIO) by approximately 4.3-fold. The EMA approved the use of Zarzio in 2008 for shortening neutropenia days after chemotherapy [29, 30]. By extrapolation, indications were broadened to other areas, such as HSC mobilization and post-transplant use of G-CSF.

In the setting of HSC mobilization, all retrospective studies conducted to date have combined the use of BIO and chemotherapy; similar outcomes to those of NEU were found both in terms of the CD34+ cell peak on day +4 and total number of CD34 +cells harvested after apheresis, supporting the use of BIO instead of NEU in all indications.

With all the weaknesses and pitfalls associated to a retrospective analysis, our study is the first one that compares the results of mobilization characteristics of NEU and BIO alone, outside of chemotherapy-based regimens, in patients with MM or lymphoma candidates for auto-HCT. The major differences were seen in those patients who fulfilled the criteria for being poor mobilizers and who were candidates to receive PLEX. In these 45 patients, the median number of CD34+ cells was significantly lower in patients receiving BIO than in those receiving NEU (2.4 vs 4.8 $\times$ 10^3/ml; p = 0.02). Moreover, the use of BIO was associated to a significant lower number of CD34+ cells collected (2.5 vs. 3.3 $\times$ 10^6 CD34+/kg; p = 0.03), and more BIO patients needed a second dose of PLEX and, eventually, a second apheresis. The only independent prognostic factor that was associated to a mobilization failure in the context of PLEX was the use of BIO, although this finding must be considered carefully because there were only five cases of mobilization failure.

Based on these results, PLEX would appear to be less efficacious when associated to BIO than to NEU, at least in the setting of G-CSF alone. Previous studies in patients are all based on chemotherapy plus G-CSF-based mobilization, rather than G-CSF alone [11–13]. One can eventually speculate that the use of chemotherapy may overcome the detrimental effect of BIO compared to NEU, although this hypothesis only applies to patients, and not to healthy donors.

The use of BIO also seemed to be detrimental for HSC collection in healthy donors. We found that 13% of the donors who received BIO needed more than one apheresis to reach the minimum level, and one of them also required PLEX.

At the present time little data are available from comparative studies on the use of PLEX in combination with biosimilar G-CSF versus originator G-CSF in poor mobilizers or patients at high risk of mobilization failure. An Italian study reported 296 patients mobilized preemptively with biosimilar G-CSF or originator G-CSF plus PLEX, as standard practice [31], 40% following chemotherapy. In contrast to our findings, the combination of biosimilar plus PLEX appeared to be more efficient in terms of primary endpoints (CD34+ cell threshold in blood

Table 3 General characteristics of "No Plerixafor" group

Variables[a]	All patients not receiving PLEX (n = 163)	Patients in NEU group not receiving PLEX (n = 105)	Patients in BIO group not receiving PLEX (n = 58)	p
Age, years (median [min–max])	54 [19–72]	55 [19–66]	56 [29–72]	ns
Weight (kg)	75 (44–121)	72.2 (44–112)	75.4 (52–121)	ns
Sex				ns
Male	80 (49%)	58 (55.2%)	22 (37.9%)	
Female	83 (51%)	47 (44.8%)	36 (62.1%)	
Basal disease				0.02
Myeloma	104 (63.8%)	70 (66.7%)	34 (58.6%)	
Lymphoma	59 (36.2%)	35 (33.3%)	24 (41.4%)	
Disease status:				ns
CR	87 (53.3%)	51 (48.6%)	36 (62.1%)	
PR	71 (43.5%)	50 (47.6%)	21 (36.2%)	
SD/active	5 (3.2%)	4 (3.8%)	1 (1.7%)	
Number of prior lines of chemotherapy				ns
0–1	113 (69.3%)	74 (70.5%)	39 (67.2%)	
2	48 (29.4%)	30 (28.5%)	18 (31%)	
3	2 (1.3%)	1 (1%)	1 (1.7%)	
Peripheral blood counts prior mobilization				
Leucocytes ($\times 10^6$/ml)	6.7 (0–17.8)	6.9 (0–17.8)	6.2 (2.9–14.2)	ns
Platelets ($\times 10^6$/ml)	247 (78–525)	224 (78–525)	253 (106–423)	ns
G-CSF dose (ug)	1380 (600–2040)	1560 (600–2014)	1560 (600–2040)	ns
CD34+ cells on day +4 ($\times 10^3$/ml)	39.8 (10.5–185)	33.4 (10.5–185)	23.7 (10.6–152)	0.03
10.1–15 $\times 10^3$/ml	28 (17.1%)	14 (15.6%)	14 (26.4%)	0.1
$> 15 \times 10^3$/ml	115 (82.9%)	76 (84.4%)	39 (73.6%)	
CD34+ cells on day +5 ($\times 10^3$/ml)	55.6 (8–244)	49.5 (8–244)	42 (9.1–223)	ns
Total CD34 + cells mobilized ($\times 10^6$/kg)	5.5 (1.1–20.7)	4.9 (1.1–20.7)	4.79 (2.1–20.6)	ns

Table 3 continued

Variables[a]	All patients not receiving PLEX (n = 163)	Patients in NEU group not receiving PLEX (n = 105)	Patients in BIO group not receiving PLEX (n = 58)	p
> 1 Apheresis procedure	19 (11.6%)	16 (15.2%)	3 (5.2%)	0.05
Mobilization failure	2 (1.2%)	2 (1.9%)	0	ns

[a] Variables in table are reported as the median with the range in parenthesis or as the number of patients with the percentage in parenthesis, unless indicated otherwise

Table 4 Multivariable analysis

Variables	Hazard ratio (95% confidence interval)	p
Risk factors for the use of PLEX (CD34+ > 10 × 10^3/ml in peripheral blood)		
Age	0.96 (0.93–0.99)	0.04
Basal disease (reference myeloma)	0.24 (0.1–0.56)	0.001
Number of prior lines (< 2)	0.32 (0.17–0.61)	0.001
Risk factors for mobilization failure (only in PLEX patients)		
Type of GSCF (reference BIO)	10.3 (1.3–77.8)	0.02

and CD34 target finally collected in apheresis),. The authors of the Italian study concluded that their data supported the standard inclusion of biosimilar filgrastim in mobilizing protocols since a stronger efficacy of the biosimilar G-CSF plus PLEX was found and, consequently, significant cost saving would be possible. Other studies have also found no differences with different GCSG plus PLEX [32], but in these studies PLEX was used in a pre-emptive manner and not, as in our study, only in cases of poor mobilization.

It is debatable if a pre-emptive use of PLEX should be worldwide indicated in predicted poor mobilizers [33–35]. Previous studies have shown that PLEX mobilization in these patients significantly increases the final total of collected CD34+ cells, thus assuring the minimum required and avoiding further apheresis procedures (and associated risks as thrombocytopenia or citrate reactions). However, this did not translate into improved long-term graft function or clinical outcomes [30], and more cost-effective analyses are needed to potentially change future guidelines for mobilization. In our clinical setting, PLEX is administered according to specific criteria based on CD34+ level in PB and final CD34 + cells yielded after apheresis, with some differences among the groups [26, 31, 32, 36].

Previous studies on cost-effective analyses in the setting of HSC mobilization are mainly based on the use of PLEX against chemotherapy plus G-CSF [35, 37]. With respect to BIO versus NEU, most studies have been designed in the setting of neutropenia after chemotherapy, with the results favoring the use of the biosimilar since non-inferiority of the biosimilar was proven [38]. On the other side, as overall outcomes in previously published studies have been equivalent between BIO and NEU, the universal use of BIO in this setting can represent a significant cost saving [12, 13]. Our cost-effective analysis also favored the use of BIO, in spite of apparent lower efficacy, and we believe this is attributable to the expensive cost of NEU (4-fold > BIO) and the small sample size.

The present study has certain limitations due to its retrospective design, small sample size, and the different number of patients in the groups being compared. However, these preliminary results deserve some attention since

Table 5 General characteristics of donors

Variables[a]	All donors (n = 56)	Donors receiving NEU (n = 33)	Donors receiving BIO (n = 23)	p
Age, years (median [min–max])	49.5 [17–75]	53 [21–73]	46 [17–75]	0.04
Weight (kg)	72 (50–119)	73 (50–104)	67 (54–119)	ns
Sex				0.05
Male	33 (58.9%)	23 (69.7%)	10 (43.5%)	
Female	23 (41.1%)	10 (30.3%)	13 (56.5%)	
Peripheral counts prior mobilization				ns
Leucocytes ($\times 10^6$/ml)	6.5 (4.1–13.7)	6.5 (4.2–13.7)	6.5 (4.1–10)	
Platelets ($\times 10^6$/ml)	221 (134–369)	210 (134–297)	238 (161–369)	
G-CSF dose (ug)	960 (600–1560)	960 (600–1560)	1080 (600–1560)	0.1
CD34+ on day +4 ($\times 10^3$/ml)	73.6 (15.3–166.2)	70 (13.3–166.2)	71.5 (22.3–156.7)	ns
CD34+ on day +5 ($\times 10^3$/ml)	100 (10–243)	97.7 (10–243)	100 (15.3–239.7)	ns
Total CD34+ mobilized ($\times 10^6$/kg)	8.3 (0.7–23.2)	7.7 (0.7–12.9)	10.7 (3–23.2)	0.02
> 1 Apheresis	3 (5.3%)	0	3 (13%)	0.03
Use of plerixafor	1 (1.7%)	0	1 (4.3%)	0.2
Mobilization failure	1 (1.7%)	1 (3%)	0	0.1

[a] Variables in table are reported as the median with the range in parenthesis or as the number of patients with the percentage in parenthesis, unless indicated otherwise

there are no prior publications, to our knowledge, reporting a comparison of these two formulations in the setting of only G-CSF-based HSC mobilization.

CONCLUSION

Based on our experience and within the setting of G-CSF-based mobilization with no prior chemotherapy, the combination of PLEX + BIO might be less efficacious than PLEX + NEU in patients defined as being poor mobilizers. These findings should be confiirmed in larger samples, ideally in prospective randomized clinical trials.

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Compliance with Ethics Guidelines. The scientific proposal was reviewed and approved by the ethical committee of the institution (ICO-IDIBELL), and all procedures were in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. All participants included in the study provided written informed consent.

Data Availability. All data generated or analyzed during this study are included in this published article.

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