Received: 1 June 2017 | Accepted: 2 June 2017

DOI: 10.1002/ajh.24817

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A comparative analysis of biosimilar vs. originator filgrastim in combination with plerixafor for stem cell mobilization in lymphoma and multiple myeloma: a propensity-score weighted multicenter approach

To the Editor:

Biosimilar G-CSFs are widely employed today for different clinical indications including hematopoietic stem cell mobilization, despite lack of robust evidence in this setting. Different single-institution retrospective studies compared mobilization kinetics of patients given biosimilar G-CSFs or originator compound, overall reporting equivalent activity.[1-3] However, extremely little evidence is available about comparative efficacy of biosimilar and originator compounds when G-CSF is combined with plerixafor to rescue patients at high risk of mobilization failure.[4]

We herein report the results of a retrospective analysis of 296 patients affected by multiple myeloma (MM), non-Hodgkin (NHL), or Hodgkin lymphoma (HL) who underwent PBSC mobilization with G-CSF and plerixafor as part of the mobilizing strategy at 22 italian centers from January 2008 to December 2016 (patient characteristics are presented in Supporting Information Table 1). G-CSF compound employed was either originator (Neupogen®, Amgen) or biosimilar filgrastim (Zarzio®, Sandoz Industrial Products; Tevagrastim®, Teva Pharmaceutical Industries). Originator or biosimilar filgrastim were administered subcutaneously at a dosage of 5 μg/kg/day (following chemotherapy) or 10 μg/kg/day (in case of steady-state mobilization). Plerixafor was given at a dosage of 240 mcg/kg body weight. Peripheral blood CD34+ (PB-CD34+) were measured at hematopoietic recovery (in case of chemo-mobilization) or at day 4 of G-CSF administration (in case of steady-state mobilization), and then daily until stem cell collection completion or failure. The threshold of PB-CD34+ cells for starting apheresis procedure was established at 20×10^6/L. Given the retrospective nature of the study, a propensity score weighted analysis was conducted in order to soften inherent limitations as imbalances between the two study groups in terms of patient and mobilization characteristics.[5]

A total of 296 patients were included in the analysis. Forty-two percent of patients ($n = 123$) were affected by MM, 49% ($n = 143$) by NHL and 9% ($n = 29$) by HL. Forty percent of patients ($n = 118$) underwent chemo-mobilization, while 60% ($n = 178$) steady-state mobilization. One hundred and ninety-seven patients (67%) received originator filgrastim combined with plerixafor (OR + PLX), while 99 patients (33%) were given biosimilar filgrastim and plerixafor (BIO + PLX). The median PB-CD34+ count before and after plerixafor administration were 8/mcl (IQR 3–12), and 33/mcl (IQR 15–58), respectively, with an average 6-fold increase.

Patients included in the BIO + PLX cohort were more likely to exceed the PB-CD34+ threshold of 5/mcl before plerixafor administration, as compared to the OR + PLX group, as evidenced by propensity score weighted analysis (weighted OR = 3.6; robust 95% CI 1.5–8.4). Further, patients receiving BIO + PLX showed higher probability of reaching the PB-CD34+ threshold of 20/mcl after plerixafor administration, as compared to the OR-PLX group (weighted OR = 6.8; robust 95% CI 2.6–17.6). Finally, patient mobilized with the BIO + PLX combination were more likely to collecting a stem cell dose of 2×10^6 CD34+/kg or higher (weighted OR = 6.1; robust 95% CI 1.9–18.9). The combination of BIO + PLX appeared to be more efficient in term of primary endpoints both in MM and lymphoma subgroups, although confidence intervals resulted quite wide, probably due to reduced sample size (Table 1). Patients who received BIO + PLX were more likely to reach the apheresis procedure as compared to OR + PLX group (weighted OR = 5.3; robust 95% CI 1.1–26.4) without any difference in the number of apheresis procedures (one or more) required to complete stem cell collection (weighted OR = 0.7; robust 95% CI 0.3–1.5). One hundred and seventy-eight patients (62%) received autologous transplant as planned, 79% of the patients who collected at least 2×10^6 CD34+/kg. The mobilization strategy (BIO + PLX or OR + PLX) did not influence the probability of performing the planned auto-SCT procedure (weighted OR = 1.5; robust 95% CI 0.7–3.4). Engraftment was successful in 97% of patients with no significant difference between the two study cohorts. T1

In the largest study comparing two different biosimilar G-CSFs and the originator drug in association with plerixafor, we observed a powerful mobilizing efficacy of the combination of biosimilar filgrastim and plerixafor, which was not inferior and, surprisingly, even more powerful as compared to the combination with originator G-CSF. Interestingly, in our series, biosimilar filgrastim resulted in higher probability of reaching the pre-plerixafor PB-CD34+ threshold of 5/mcl as compared to originator G-CSF. Further, BIO + PLX was associated with an increased likelihood to get to the threshold of 20/mcl and, as a direct consequence, to collect at least

J_ID: Customer A_ID: AJH24817 Cadmus Art: AJH24817 Ed. Ref. No.: AJH-17-0662 Date: 13-July-17 Stage: Page: 2

TABLE 1 Efficacy of BIO + PLX as compared to OR + PLX on stem cell mobilization with regards to primary endpoints

Panel A: descriptive analysis		
PB-CD34+ count pre-plerixafor administration		
	PB-CD34+ before PLX Median (IQR)	**PB-CD34+ before PLX >5/mcl % of patients**
BIO+PLX cohort	10.0 (6.0–16.0)	77%
OR+PLX cohort	5.3 (2.0–9.0)	51%
PB-CD34+ count after plerixafor administration		
	PB-CD34+ after PLX Median (IQR)	**PB-CD34+ after PLX >20/mcl % of patients**
BIO+PLX cohort	50.2 (30.0–71.0)	88%
OR+PLX cohort	24.0 (12.0–48.0)	56%
CD34+/Kg body weight collected in up to 4 apheresis procedures		
	CD34+/Kg collected Median (IQR)	**CD34+/Kg collected >2 × 10^6 % of patients**
BIO+PLX cohort	4.2 (3.0–5.9)	92%
OR+PLX cohort	4.0 (2.5–6.8)	82%

Panel B: propensity score weighted logistic regression analysis			
Probability of exceeding the PB-CD34+ threshold of 5/mcl (pre-plerixafor) BIO+PLX cohort	**weighted OR**	**robust 95% CI**	
Entire sample	3.6	1.5	8.4
Multiple myeloma patients	6.9	2.0	23.9
Lymphoma patients	*2.4*	*0.8*	*7.0*
Probability of exceeding the PB-CD34+ threshold of 20/mcl (after plerixafor) BIO+PLX cohort	**weighted OR**	**robust 95% CI**	
Entire sample	6.8	2.6	17.6
Multiple Myeloma patients	4.3	1.3	14.4
Lymphoma patients	10.5	2.3	48.3
Probability of collecting at least 2 × 10^6 CD34+/Kg BIO+PLX cohort	**weighted OR**	**robust 95% CI**	
Entire sample	6.1	1.9	18.9
Multiple myeloma patients	*5.5*	*0.6*	*50.4*
Lymphoma patients	6.9	1.8	26.5

2 × 10^6 CD34+/kg, as compared to OR + PLX. Our analysis confirms previous evidence of noninferiority of biosimilar to originator filgrastim,[6] and suggests an even higher mobilizing power of BIO + PLX as compared to OR + PLX. Considering the constant improvement of pharmaceutical manufacturing techniques it might come as no surprise that a newer drug which is required to be "at least not inferior" actually turns out to be more efficient than the older one. It should be noted, however, that patients given the BIO + PLX combination underwent stem cell mobilization significantly more recently as compared to OR + PLX group; this might have somehow influenced data analysis, as it could be speculated that advancements in recent years brought a significant improvement in apheresis techniques, mobilization strategies and maybe even plerixafor use.

In conclusion, the combination of biosimilar filgrastim and plerixafor appears to be at least equally and might be more effective as compared to originator filgrastim and plerixafor for stem cell mobilization in patients at high risk of mobilization failure. This data strongly support standard inclusion of biosimilar filgrastim in mobilizing protocols even in the challenging setting of patients who mobilize poorly, as significant cost saving seems to be accompanied by strong efficacy.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.