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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.

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,

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

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 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.

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Deformability of transfused red blood cells is a potent effector of transfusion-induced hemoglobin increment: A study with β-thalassemia major patients

To the Editor:

In the current routine, blood donations are subjected to testing of blood type and pathogenic gents on day of donation, and the supply of packed red blood cells (PRBC) units for transfusion is conducted primarily according to storage duration, namely by the first-in-first-out (FIFO) criterion. However, the actual functionality of the transfused PRBC, namely their capacity to effect the expected transfusion outcome is ignored. This is especially pertinent to patients with chronic anemia, like β-thalassemia major (TM), who are treated with life-long frequent transfusions (of one or two units) every 2–4 weeks. The transfused RBC are aimed at raising the hemoglobin (Hb) level in the recipients' blood. However, RBC have unique mechanical properties, deformability in particular, which play a major role in blood circulation and in the RBC survival. In a recent study[1] with TM patients, we have shown, for the first time in humans, that the transfusion-induced change in the recipients' skin blood flow strongly correlated with the deformability of the transfused PRBC.

In the present study, we examined the effect of transfused RBC deformability on the immediate transfusion outcome, as expressed by the increase in the recipients' Hb (ΔHb), as well as the time interval between consecutive transfusions (TIBT).

Employing TM patients for this study has specific advantages; TM patients are treated with life-long frequent transfusions (every 2–4 weeks). Therefore, testing the effect of repeated, consecutive transfusions in the same patient, having about the same baseline throughout the study, provides solid grounds for attributing the observed effect to the properties of the transfused PRBC units. In addition, TM patients at the Hadassah Hospital Thalassemia Clinic are routinely given PRBC units stored for up to about 10 days, when the potential storage-lesion is insignificant.

Twenty-four TM patients were employed; their characteristics are summarized in Supporting Information Table S1. The transfusion-induced changes in the recipients' hemoglobin (ΔHb) and hematocrit (ΔHct) were determined 10 minutes after the transfusion completion.

The results clearly showed that:

1. ΔHb exhibited a highly significant positive correlation with RBC deformability: The transfusion outcome was analyzed vs. various parameters derived from deformability distribution of the PRBC. It was found that ΔHb, shown in Figure 1, as well as ΔHct (Supporting Information Table S2), were best correlated with the percent of low deformable cells (% LDFC), with highly significant inverse dependence on this parameter.
2. In addition to the immediate increase in the recipients' hemoglobin, an important criterion of the transfusion efficacy in TM patients is the time interval between consecutive transfusions (TIBT). As noted above, TM patients are treated with frequent (every 2–4 weeks) transfusions, and the longer is the TIBT, the better is the transfusion outcome. In the present study we have found that PRBC with low level of rigid RBC yields a longer interval between two consecutive transfusions (> 21 days), suggesting that RBC with good deformability would endure longer in the circulation and enable less frequent consecutive transfusions (Supporting Information Figure S2).