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Biosimilars of filgrastim in autologous stem cell transplantation: certain differences for myeloma patients only

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RhuG-CSF reduces the duration of neutropenia induced by chemotherapies. The most frequent drug used for this indication is filgrastim (initially Neupogen[®]-AMGEN SA). Filgrastim biosimilars have been developed through modifications of the native molecule [1]. Defined by WHO, a biosimilar is 'a biotherapeutic product which is similar in terms of quality, safety, and efficacy to an already licensed reference biotherapeutic product'. RhuG-CSFs are produced from living cells, which means they require different production processes and present an increased possibility of immunogenicity (compared to purely 'chemically' processed molecules). The production costs of these drugs are much lower, making them interesting therapeutic tools to reduce medical costs. Furthermore, the efficiency of biosimilars of filgrastim seems comparable to that of native filgrastim, allowing their use in the same therapeutic indications [2–5].

There are limited data concerning the use of biosimilars of filgrastim in autologous stem cell transplantation (ASCT) [6–9]. We aimed to evaluate G-CSF efficiency and safety (based on hemograms, transfusion needs, and complications) of two biosimilars (Zarzio[®] and Ratiograstim[®]) compared to those of Neupogen[®] for our patients who underwent ASCT. A comparison of the three drugs in this indication is presented below.

Since 2008, data relating to all patients who underwent ASCT at our center to treat lymphoma or myeloma were collected. The parameters studied in this article have been previously published [7,10]. All the patients signed an institutional informed consent form prior to the harvest of peripheral stem cells (PROMISE program). Patients treated between April 2008 and February 2010 received Neupogen[®] (Amgen-SA, N-group). The next group of patients, from March 2010 to May 2012, were treated with Ratiograstim[®] (Ratiopharm GmbH, R-group). The last group of patients, from June 2013 to November

2014, received Zarzio[®] (Sandoz GmbH, Z-group) (ZAPA – Zarzio in Post-ASCT – study).

Patients with lymphoma received a BEAM conditioning regimen, and myeloma patients received a high dose of Melphalan infusion [11,12]. The reinjections of peripheral stem cells (PSC) were performed at least 25 hours after the completion of the Melphalan infusion. All patients received the same intra-venous daily dose of 30 MUI regardless of their weight. The stimulation started on day 5 after ASCT and ended when patients were at a minimum of 1 giga-liter/l of polymorphonuclear neutrophils. We performed hemograms every other day. Patients were transferred to the Intensive Care Unit (ICU) in cases of hypoxic pneumopathy, septic shock, cardiogenic shock, or acute neurological deficiency.

The Student's t-test and Chi-squared test were applied using the R-project (3.1.2 version, BiostatGV website, hosted by the Institute for Statistics and Mathematics of Wirtschaftsuniversität Wien). Statistical significance was declared if the *p* value was less than 0.05, and each value is expressed plus or minus the standard deviation.

We collected data on 187 ASCT procedures (88 myelomas and 99 lymphomas) from 114 men and 73 women. Neupogen[®] (N), Ratiograstim[®] (R) and Zarzio[®] (Z) were, respectively, used for 51, 74, and 62 patients. The characteristics of the patients are shown in Table 1. The characteristics at the time of admission for the ASCT procedure were similar for patients in the myeloma and lymphoma groups, and the median ages were 60 and 57 years, respectively, while in the Z-group, patients were older (*p* = 0.01 in the myeloma subgroup).

For the myeloma group, the mean number of injections of rhuG-CSF was approximately seven. The median duration of hospitalization was 16 days, compared to only 15.2 days for the Z-group (*p* = 0.06) despite the fact that the N-drug significantly reduced the duration of neutropenia (5.8 days, *p* = 0.04) and thrombocytopenia

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Table 1. Characteristics of the patients at the time of admission for ASCT and in post-ASCT phase.

	Multiple myeloma				Lymphoma			
	Neupogen®	Ratiograstim®	Zarzio®	<i>p</i>	Neupogen®	Ratiograstim®	Zarzio®	<i>p</i>
Number of patients (nb)	25	30	33		26	44	29	
Sex ratio	1.5	1.1	1.5	ns	2.2	1.3	2.2	ns
Age (y)	57.7 (45–68)	55.4 (36–66)	62.4 (48–68)	0.01	51 (26–66)	50.8 (15–70)	55.8 (21–70)	ns
Hemogram at admission								
Leukocytes (giga/L)	4.3 (1.9–6.6)	5.2 (2–9.5)	4.8 (2.6–9.5)	ns	4.5 (1.9–8.2)	4.5 (1–8.3)	4.9 (1.8–10.1)	ns
Hemoglobin (g/dL)	12 (8.9–14.5)	12.2 (8.2–16.9)	12.2 (9.3–14.3)	ns	11.4 (9.1–13.3)	11.4 (9.1–15.7)	11 (8.2–13.9)	ns
Platelets (giga/L)	259 (138–369)	218 (78–361)	241 (20–470)	ns	199 (45–426)	199 (75–429)	218 (50–575)	ns
Number of CD34+ cells infused (10 ⁶ /kg)	3.6 (1.6–7.4)	3.67 (2.2–6.8)	3.17 (1.3–9.7)	ns	4.1 (1.7–12.3)	4.1 (2.2–7.5)	3.2 (1–6.3)	ns
Nb of days of rhuG-CSF (d)	6.9 (5–9)	7.7 (1–16)	7.1 (1–10)	ns	7.3 (6–10)	7.3 (4–12)	8.1 (4–13)	ns
Duration of parameters (d)								
Hospitalization	16 (14–19)	17.6 (13–42)	15.7 (13–22)	0.06	24.2 (19–31)	24.2 (17–64)	23.4 (16–43)	ns
Leukocytes <1 giga/L	5.8 (4–8)	7 (4–16)	6.7 (3–12)	0.04	10.8 (8–14)	10.8 (5–19)	10.4 (3–14)	ns
Hemoglobin <9 g/dL	1.8 (0–7)	3.9 (0–42)	2.1 (0–15)	ns	7.7 (0–15)	7.7 (0–33)	9.9 (0–33)	ns
Platelets <50 giga/L	5.2 (2–9)	8.1 (1–40)	5.7 (0–14)	0.05	14.2 (6–21)	14.2 (7–55)	13.7 (2–39)	ns
Transfusions of RBC								
Patients (nb/%)	5 (20)	10 (33)	8 (24)	ns	23 (88)	37 (84)	24 (83)	ns
Units (nb)	0.5 (0–4)	0.8 (0–4)	0.5 (0–4)	ns	2.4 (0–8)	2.4 (0–9)	3.4 (0–14)	ns
Transfusions of platelets								
Patients (nb/%)	24 (96)	29 (97)	28 (85)	ns	26 (100)	44 (100)	28 (97)	ns
Units (nb)	1.4 (0–5)	2.3 (0–12)	1.2 (0–5)	0.06	4 (2–9)	4 (2–17)	5.8 (0–36)	ns
Bone pain (nb/%)	6 (24)	9 (30)	2 (6)	0.03	0	3 (7)	0	ns
Fever								
Patients (nb/%)	18 (72)	22 (73)	23 (70)	ns	26 (100)	44 (100)	28 (97)	ns
Duration (d)	2.1 (0–8)	1.9 (0–8)	1.5 (0–8)	ns	5.8 (1–16)	5.8 (1–16)	5.3 (0–15)	ns
ICU transfer (nb/%)	1 (4)	2 (7)	1 (3)	ns	1 (4)	4 (9)	5 (17)	ns
Death under d100 (nb/%)	0	0	0	ns	2 (8)	1 (2)	1 (3)	ns

Results are expressed as mean and extreme values.

Nb: number; ns: non-significant ($p > 0.05$); RBC: red blood cells. Statistical results who reached significance (between 0.05 and 0.1) were notified in the table.

(5.2 days, $p = 0.05$). Transfusions of RBC or platelets were performed in 26.1% (mean = 0.6 unit/patient) and 92% (mean = 1.6 units/patient) of patients, respectively. Patients receiving the Z-drug had reduced requirements for platelet units ($n = 1.2$ units/patient, $p = 0.06$), whereas there was no difference in the RBC requirement. Bone pain was reported by 20.5% of the patients but only by 6% of the patients treated by the Z-drug ($p = 0.03$). Fever (temperature greater than 38 °C) was observed in 71.6% of myeloma patients, without a difference between the three groups. However, only four patients were transferred to the ICU, and none of them died within 100 days of ASCT.

Concerning the lymphoma group, the median duration of hospitalization was 22 days, and the mean number of rhuG-CSF injections was approximately 7.5. No significant differences were observed between the three drugs in terms of the duration of hospitalization, the duration of cytopenia, and RBC or platelet requirements (despite a longer duration of anemia in the Z-group, $n = 9.9$ versus 7.7 days and increased need for RBC, $n = 3.4$ versus 2.4). Transfusion of platelets was prescribed for 85% of the patients, whereas 99% of them required RBC units. Bone pain was rarely expressed and only related to the R-group (3/44, 7%). Fever was observed in all patients without a difference in duration. Ten percent of the patients were transferred to the ICU with a maximum of 17% in the Z-group but with a low overall death rate (4%).

Bacteremia was identified in 4 out of 51 patients (7.8%) in the N-group, 14 out of 74 patients (18.9%) in

the R-group and 11 out of 62 patients (17.7%) in the Z-group ($p = 0.2$). In the N-group, all the bacteria were gram-positive cocci, whereas the majority of bacteria found in the two other groups were gram-negative bacilli ($R = 12/14$, 85.7% and $Z = 10/11$, 90.9%) with half of cases related to *E. coli* positivity.

Since 2008, more than ten rhuG-CSF biosimilars have been available, and the majority of them have derived from the original filgrastim-Neupogen® (Amgen-SA). Although these drugs are available, their use should be carefully considered, especially in situations where safety and efficacy are being extrapolated [13].

Few studies have been published on the use of rhuG-CSF biosimilars during the ASCT procedure. To date, no phase 3 trial data are available. Reported data tend to indicate a similarity (efficacy and toxicity) between biosimilars of filgrastim and the original filgrastim during mobilization and post-ASCT phases [6–9,14,15].

At our center, we collected all of the data related to ASCT for patients treated for myeloma or lymphoma. All of the patients were treated in accordance with the same process as follows: the same dose regardless of weight, the same mode of administration and at the same time following PSC reinjection. However, we consecutively used three rhuG-CSF drugs in the same indication and aimed to report our experience concerning the use of rhuG-CSF biosimilars.

As expected, patients with myeloma were older than patients with lymphoma. In each group, patients receiving Zarzio® were also older, perhaps because the age

limit for performing ASCT at our institution has increased through the years (the patients in the Z-group are the oldest). This was not detrimental to the study because these patients did not have greater difficulties in overcoming aplasia.

We only observed differences on the following studied parameters in the myeloma group: duration of cytopenia, platelet requirements, and bone pain. Neupogen® seems to be the most efficient for reducing cytopenia in patients with myeloma (no difference in lymphoma group). In contrast, Zarzio® induced less bone pain and reduced the requirement for platelet units in this same group. The differences observed between the three rhuG-CSFs are intriguing. As the procedure was identical through the years, we can therefore assume that they do not have the same intrinsic quality. No difference was observed in the lymphoma group, perhaps due to the more intensive conditioning regimen.

Furthermore, bacteremia was less frequent in the N-group (possibly a less aggressive profile of neutropenia), and all the bacteria were gram-positive cocci, whereas there were gram-negative bacilli in the two other groups. Pinana et al. [16] identified a longer duration of leucopenia as the principle risk factor for bacteremia, and this was also true for the incidence of gram-positive bacilli.

In this study, the comparison of the native filgrastim with two of its biosimilars in a large cohort of patients requiring ASCT showed that these three drugs could be safely used in this indication without any major disparity. However, a number of interesting differences were observed between the drugs but only in the myeloma group. Of course, we agree that only a prospective multi-center and double-blind (filgrastim biosimilar vs filgrastim Neupogen®) trial would be able to demonstrate the non-inferiority of these biosimilars in this indication. Such a trial should automatically be associated with a medico-economic analysis, because of the use of biosimilars would induce an important and significant reduction in hospitalization costs.

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