Lenograstim 5 μg/kg is not superior to biosimilar filgrastim 10 μg/kg in lymphoma patients undergoing peripheral blood stem cell mobilization after chemotherapy: preliminary results from a prospective randomized study

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BACKGROUND: Randomized trials comparing chemomobilization efficiency between lenograstim and biosimilar filgrastim are lacking. Our previous retrospective study suggested that lenograstim could be more effective than biosimilar filgrastim when used at the same conventional dosage (5 μg/kg) only in lymphoma patients undergoing peripheral blood stem cell mobilization. We planned a prospective randomized study comparing lenograstim 5 μg/kg with biosimilar filgrastim 10 μg/kg to verify the hypothesis of lenograstim superiority even at half the dosage (stress test). Herein we report data after enrolling 60% of planned patients.

STUDY DESIGN AND METHODS: From October 2014 to November 2017, a total of 42 of 70 planned patients with lymphoma were randomly assigned to receive lenograstim 5 μg/kg (21) or biosimilar filgrastim 10 μg/kg (21). Patients were stratified according to treatment line at the time of mobilization (1 or ≥2). Primary endpoint was the rate of achievement of the CD34+ cell collection target dose (≥4 × 10^6/kg). An improvement by 23% was expected to validate the hypothesis of lenograstim superiority.

RESULTS: The two cohorts were balanced for all the baseline features. We observed an identical rate of patients able to reach the targeted CD34+ cell dose and of mobilization failures (90.4 and 4.8% in both cohorts) and a perfect equivalence in any of the secondary collection outcomes. The hypothesis of lenograstim superiority was not corroborated at interim analysis.

CONCLUSION: Lenograstim at conventional dosage has failed to demonstrate its superiority over biosimilar filgrastim at double the dosage at interim analysis in their first head-to-head trial.

ABBREVIATIONS: ANC = absolute neutrophil count; PBSC(s) = peripheral blood stem cell(s).

Current best approach for peripheral blood hematopoietic stem cell (PBSC) mobilization and collection in lymphoma patients is the combination of chemotherapy and granulocyte-colony-stimulating factors (G-CSF). The main published guidelines consider acceptable both lenograstim and filgrastim at the dosage of at least 5 μg/kg after chemotherapy,1-3 where the vast majority of the data on an in vivo equivalence between filgrastim and lenograstim arise from retrospective or randomized studies on populations including patients with inhomogeneous diagnosis. From this point of view, there are two major concerns. First, the level of evidence delivered by retrospective studies is low. Second, comparing the mobilization outcomes by holding together cohorts of myeloma, lymphoma, leukemia, and solid tumor patients, which are characterized by such a
profoundly different therapeutic approach and load, could determine a difficulty in appreciating possible differences between the two formulations of G-CSF in the single subset. In vitro studies conducted since the mid-1990s have shown that glycosylation of G-CSF makes the molecule more stable to changes in pH, temperature, and proteolysis; increases the ability to stimulate the colony growth of both purified CD34+ and unmanipulated PBSCs; improves the priming effect on superoxide production by human neutrophils; and determines a lower activation of the RhoA gene pathway. However, to date, there are only sporadic experiences in vivo of some form of superiority of lenograstim compared to originator filgrastim in randomized or prospective mobilization trials.4-6 Since 2005, biosimilar formulations of filgrastim have become available in Europe and then in the United States on the basis of comparable quality, safety, and efficacy as the originator product in any of the approved indications. In the past years, several studies have been carried out with the aim to compare biosimilar and originator filgrastim in PBSC mobilization and autologous stem cell transplant, all confirming a substantial equivalence in terms of efficacy and safety.7-10 However, there are only few retrospective studies comparing lenograstim with biosimilar filgrastim in hematologic patients undergoing PBSC mobilization,11-14 while randomized trials focusing exclusively on lymphoma patients are lacking. Our recently published retrospective data suggested that only in lymphoma but not in myeloma patients lenograstim was more effective than biosimilar filgrastim when used at the same dosage of 5 μg/kg for PBSC mobilization, with a comparable safety profile.12 Based on these considerations, we planned a prospective randomized study comparing, after chemotherapy, lenograstim at the conventional dosage of 5 μg/kg body weight with biosimilar filgrastim at the highest unconventional dosage of 10 μg/kg body weight with the aim to verify the hypothesis of lenograstim superiority in lymphoma patients undergoing PBSC mobilization even at half the dosage. Herein we report data from interim analysis carried out after enrolling 60% of planned patients.

MATERIALS AND METHODS

Patients
From October 2014 to November 2017, a total of 42 patients with lymphoma (non-Hodgkin’s n = 32, Hodgkin’s n = 10) were randomly assigned to receive lenograstim 5 μg/kg (n = 21) or biosimilar filgrastim 10 μg/kg (n = 21) for PBSC mobilization. Patients were allocated to each arm on the basis of a standard randomization carried out by the principal investigator and stratified according to treatment line at the time of PBSC mobilization (after a first-line treatment or after a salvage treatment for relapsed or refractory disease). The study was conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines, and all patients signed a specific informed consent for G-CSF plus chemotherapy and/or plerixafor administration and granting sensitive data use for scientific purposes. We included into the study lymphoma patients aged 18 years or older eligible for PBSC collection after a mobilization chemotherapy. Patients who failed a previous attempt of PBSC collection or defined as predicted poor mobilizers by the Gruppo Italiano Trapianto di Midollo Osseo (GITMO) score were excluded.15

Rationale for choosing different G-CSF doses in the two arms
A quantity of 5 μg/kg body weight G-CSF has to date been considered the optimal dose of any G-CSF in chemomobilization, because there is no clear evidence of a linear increase in the efficiency of mobilization beyond this dose. In the lenograstim arm, a conventional dosage of 5 μg/kg/day was chosen to reach a CD34+ cell collection dose of at least 4 × 10^6/kg, perfectly in accordance with the officially recommended dose of 150 μg/m² (equivalent to 5 μg/kg body weight) for the chemomobilization and with our previous old study in which the dose of 5 μg/kg/day was as effective as 10 μg/kg/day in lymphoma patients.16 In the biosimilar filgrastim arm, an unconventional dosage of 10 μg/kg/day was chosen to test the hypothesis of lenograstim superiority under conditions of maximum stress imposed through comparison with highest doses, even if we were aware it was unlikely that such a double dose could boost mobilization in this arm.

Study endpoints
The primary endpoint of the study was the rate of achievement of the CD34+ cell collection target dose (at least 4 × 10^6/kg). Secondary endpoints were as follows: 1) the rate of mobilization failure (“nonmobilizers”), 2) the rate of patients achieving a peak number of circulating CD34+ cells mobilized under G-CSF of at least 20 × 10^6/L, 3) the rate of patients requiring “preemptive” plerixafor administration plus G-CSF because of a peak number of circulating CD34+ cells mobilized under G-CSF between 5 × 10^6 and 19 × 10^6/L (“poor mobilizers”), 4) the peak of mobilized circulating CD34+ cells × 10^6/L, 5) the duration of G-CSF administration, 6) the number of performed apheresis procedures, 7) the safety, and 8) the hematologic recovery after transplant.

Statistical analysis
The study was powered on the basis of the primary endpoint, the rate of achievement of the CD34+ cell collection target dose (at least 4 × 10^6/kg). The sample size
calculation was based on our previous study, where the percentage of patients able to reach the planned CD34+ cell dose was 96% with lenograstim and 73% with biosimilar filgrastim both administered at the same dosage of 5 µg/kg/day. To verify the alternative hypothesis (H1) that lenograstim was able to increase by 23% (from 73% to 96%) the percentage of patients reaching the planned CD34+ cell dose even at half the biosimilar filgrastim dosage, against the null hypothesis (H0) of equal proportions, with a power of 80% at a significance level of 5% (with two-sided test), it was necessary to include in the study a total of 70 patients, 35 for each group. In November 2017, we planned an interim analysis on the first 42 enrolled patients into the study. Data were analyzed by computer software (Statistical Package of Social Sciences, Version 20.0, SPSS, Inc.). Baseline characteristics of the two cohorts of patients were compared using the chi-square test and t tests for dichotomous and continuous variables, respectively. Primary and secondary endpoints of the study were also evaluated using the chi-square test and t tests for dichotomous and continuous variables, respectively. Two-sided p values of not more than 0.05 were considered as significant.

PBSC mobilization and collection

Mobilization chemotherapy regimen was chosen on the basis of hematologic diagnosis according to local policy and current guidelines. Lenograstim and biosimilar filgrastim were administered subcutaneously as a single dose at daily dosages of 5 and 10 µg/kg body weight, respectively, starting on Day +1 from the end of chemotherapy. When the white blood cell (WBC) count returned to at least 1 × 10^9/L, for each patient circulating CD34+ cells were measured by flow cytometry every day until the number of these cells was considered adequate. The threshold of circulating CD34+ cells for starting leukapheresis was 20 × 10^6/L. Patients with a peak (daily monitoring) of circulating CD34+ cells between 5 × 10^6 and 19 × 10^6/L were considered poor mobilizers and therefore eligible for preemptive plerixafor administration in adjunction to G-CSF (0.24 mg/kg/day 6 hr before leukapheresis). Patients with a peak of circulating CD34+ cells lower than 5 × 10^6/L were considered nonmobilizers and therefore not eligible for preemptive plerixafor. The target dose of CD34+ cells to be harvested was at least 4 × 10^9/kg. The continuous-flow device used for leukapheresis was Fresenius COMTEC (Fresenius KABI AG). The apheresis product obtained was analyzed for the count of CD34 cells by flow cytometry (protocol used—logic gate ISHAGE subsequently modified in a single platform from EWGCCA, FACSCalibur flow cytometer, BD) and then cryopreserved within 24 hours from harvest in a 10% DMSO and stored in vapor or liquid nitrogen at temperature lower than −150°C.

RESULTS

Baseline patients’ features are reported in Table 1. As shown, the two cohorts of patients were comparable for all the considered characteristics (sex, median age and weight, diagnosis, marrow involvement, diabetes, disease phase at PBSC collection, median number of previous treatment lines, previous radiotherapy, and mobilization chemotherapy). Table 2 shows the PBSC collection outcomes. The hypothesis of a lenograstim superiority was not validated, since we observed an identical rate of patients able to intercept the target of CD34+ cell planned dose (90.4% in both cohorts; p = 1). Moreover, we also observed an identical rate of mobilization failures (4.8% in both cohorts; p = 1) and a similar rate of patients needing plerixafor administration due to a suboptimal level of CD34+ cells × 10^6/L at peak under G-CSF (23.8% in lenograstim vs 19% in biosimilar filgrastim group; p = 0.705). Median number of CD34+ cells × 10^9/kg collected at first leukapheresis was similar between the two cohorts of patients (6.67 × 10^9/kg for lenograstim vs. 6.61 × 10^9/kg for biosimilar filgrastim group; p = 0.805). Finally, median days of G-CSF administration, median number of circulating CD34+ cells × 10^6/L at leukapheresis, transfusion needs and infectious complications during mobilization chemotherapy were similar between the two cohorts of patients (Table 2). Differences in terms of drug-related adverse events were not observed, with no reported serious adverse events. As for posttransplant hematologic recovery, so far 11 patients in the lenograstim cohort and 11 in the biosimilar filgrastim cohort underwent autologous stem cell transplant. The times to absolute neutrophil count (ANC) and platelet (PLT) count recovery were 12 and 14 days, respectively, in both cohorts of patients, where the recovery was defined as ANC more than 500 × 10^3/L and PLT count more than 20 × 10^9/L in three consecutive checks.

DISCUSSION

Lenograstim and filgrastim are currently considered as equivalent for PBSC collection after mobilization chemotherapy in lymphoma patients in the main published guidelines. The European Medicines Agency and US Food and Drug Administration made available biosimilar formulations of filgrastim on the basis of comparable quality, safety, and efficacy as the originator product in any of the approved indications. However, randomized studies comparing lenograstim with biosimilar filgrastim are so far lacking; the only published comparisons are retrospective experiences which report an equivalence between the two G-CSF formulations. From our
previously published retrospective study, we suggested that lenograstim was more effective than biosimilar filgrastim at the same dosage in lymphoma but not in myeloma patients undergoing mobilization chemotherapy and PBSC collection.\textsuperscript{12} We hypothesized that the superior efficacy of lenograstim in lymphoma patients could found the basis in the glycosylated nature of this molecule, rather than in biosimilar formulation of filgrastim, with lymphoma patients having a greater previous chemotherapeutic load compared with myeloma and being speculatively more sensitive to the little differences between glycosylated and nonglycosylated formulations of G-CSF in stem cell mobilization capacity. In several preclinical studies it has been shown that lenograstim is able to preserve the functional status of mobilized cells better than filgrastim\textsuperscript{17,18} and that its glycosylation permits to maintain the cell morphology and motility in response to extracellular signals.\textsuperscript{17-20} There are at least three groups in addition to our that have suggested in randomized or prospective trials a superiority of lenograstim over originator filgrastim in the mobilization of hematopoietic progenitors in terms of faster mobilization\textsuperscript{4} or equal efficacy with

\begin{table}
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\caption{Baseline characteristics at mobilization according to received G-CSF formulation*}
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\hline
Variable & Lenograstim 5 $\mu$g/kg (n = 21) & Biosimilar filgrastim 10 $\mu$g/kg (n = 21) & \textit{p} value \\
\hline
Age (years), median (range) & 54 (23-65) & 57 (19-66) & 0.850 \\
Sex, male/female & 11/10 & 10/11 & 0.758 \\
Diagnosis & & & \\
Non-Hodgkin’s lymphoma & 14 (66.7) & 18 (85.7) & 0.277 \\
Hodgkin’s lymphoma & 7 (33.3) & 3 (14.3) & \\
Marrow involvement & 0 & 0 & 1 \\
Diabetes & 0 & 1 (4.8) & 0.311 \\
Disease phase & & & \\
First-line & 9 (42.9) & 10 (47.6) & 0.757 \\
Salvage & 12 (57.1) & 11 (52.4) & \\
Lines of chemotherapy & 2 (1-4) & 2 (1-2) & 0.270 \\
Radiotherapy (%) & 1 (4.8) & 0 & 0.311 \\
Body weight (kg) & 72 (48-92) & 67 (48-95) & 0.679 \\
Chemotherapy† & & & \\
Cytarabine-based & 13 (62) & 12 (57.1) & \\
Ifosfamide-based & 4 (19) & 8 (38.1) & \\
Etoposide-based & 4 (19) & 1 (4.8) & \\
\hline
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* Data are reported as median (range) or number (%).
† Rituximab was administered in association with chemotherapy in CD20+ B-cell lymphomas.
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\begin{table}
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\caption{PBSC collection outcomes according to received G-CSF formulation*}
\begin{tabular}{|l|c|c|c|}
\hline
Variable & Lenograstim 5 $\mu$g/kg (n = 21) & Biosimilar filgrastim 10 $\mu$g/kg (n = 21) & \textit{p} value \\
\hline
Patients achieving the CD34$^+$ cell target dose ($\geq$4 $\times$ 10$^6$/kg) & 19 (90.4) & 19 (90.4) & 1 \\
Patients achieving a suboptimal CD34$^+$ cell dose ($<4$ $\times$ 10$^6$/kg) & 1 (4.8) & 1 (4.8) & 1 \\
Mobilization failures (nonmobilizers) & 1 (4.8) & 1 (4.8) & 1 \\
Patients with peak of mobilized PB CD34$^+$ cells ($\times$10$^6$/L) under G-CSF & & & 0.931 \\
<5 (nonmobilizers $\rightarrow$ no apheresis) & 1 (4.8) & 1 (4.8) & \\
5-19 (poor mobilizers $\rightarrow$ plerixafor + G-CSF $\rightarrow$ apheresis) & 5 (23.8) & 4 (19) & \\
$\geq$20 & 15 (71.4) & 16 (76.2) & \\
Patients needing “on-demand” plerixafor (poor mobilizers) & 5 (23.8) & 4 (19) & 0.705 \\
Number of collected CD34$^+$ cells $\times$ 10$^6$/kg & 6.67 (1.65-15.3) & 6.61 (3.46-18.5) & 0.805 \\
Peak of mobilized PB CD34$^+$ cells ($\times$10$^6$/L)† & 57.5 (14-238) & 68 (22-264) & 0.221 \\
Administration of G-CSF (days) & 9 (6-15) & 9 (5-16) & 0.132 \\
Number of leukapheresis procedures & 1.33 (±0.57) & 1.14 (±0.47) & 0.251 \\
Processed volumes (mL) & 15879 (±6680) & 13491 (±6719) & 0.267 \\
Patients receiving antibiotics for fever and/or infection & 4 (19) & 6 (28.6) & 0.469 \\
Number of RBC transfusions & 1.48 (±1.6) & 1.71 (±2) & 0.675 \\
Number of PLT transfusions & 1 (0-3) & 1 (0-6) & 0.478 \\
Hematologic recovery after autologous stem cell transplant & n = 11 & n = 11 & \\
Days to ANC $>$ 500 $\times$ 10$^3$/L & 12 (9-16) & 12 (9-29) & 0.351 \\
Days to PLT count $>$ 20 $\times$ 10$^9$/L & 14 (10-27) & 14 (9-37) & 0.778 \\
\hline
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* Data are reported as number (%), median (range), or mean (±SD).
† Preapheresis data.
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reduced doses in steady state or greater collection efficiency. In this study, to the best of our knowledge the first prospective randomized trial comparing lenograstim and biosimilar filgrastim focusing exclusively on patients with lymphoma, we aimed to demonstrate that, after chemotherapy, a conventional dosage of lenograstim (5 µg/kg body weight) was more effective for PBSC mobilization even if compared with a higher unconventional dosage of biosimilar filgrastim (10 µg/kg body weight), hypothesizing a functional superiority of lenograstim in lymphoma patients also under conditions of maximum stress imposed through comparison with a double dose of filgrastim. Although our hypothesis was not corroborated at interim analysis carried out after enrolling approximately two-thirds of patients out of initial planned sample size, our preliminary results are, however, noteworthy, since they clearly show for the first time in a randomized trial that there are not significant differences between lenograstim and biosimilar filgrastim in any of the collection outcomes measured, including the in vivo demonstration of the equivalence of the collected apheresis product quality evaluated by the time to engraftment after transplant.

The question remains unanswered about whether in the exclusive setting of patients with lymphoma, considering these patients the most sensitive target to demonstrate a hypothetical difference between the two G-CSF variants, lenograstim is superior or equivalent to biosimilar filgrastim when both administered at the same conventional dosage of 5 µg/kg body weight. From this point of view, on the one hand, it should be considered amending the dose of biosimilar filgrastim bringing it to 5 µg/kg body weight, to test the hypothesis of a superiority of lenograstim over biosimilar filgrastim both administered at the same conventional dose of 5 µg/kg body weight. In this way, the statistical considerations would be the same as in the present trial, assuming that the higher doses of biosimilar filgrastim in this study have been able to abolish the gap with lenograstim shown in our previous retrospective study (approx. 20% of target dose achievement rate), although this assumption is most unlikely, because 5 µg/kg body weight is already considered the optimal dose of G-CSF independent of its variant. On the other hand, the evidence-based conclusive demonstration of equivalent efficacy between lenograstim and biosimilar filgrastim in this setting should only be provided through an appropriate noninferiority prospective randomized study. For such a study of noninferiority between lenograstim and biosimilar filgrastim both administered at the same dose of 5 µg/kg body weight, taking as reference the percentage values of achievement of the collection target obtained in this study (90%), assuming that filgrastim 5 µg/kg will work as well as filgrastim 10 µg/kg has worked in our present study, and assuming an equivalence delta equal to 5%. 446 patients for each arm should be recruited. It is clear that such a noninferiority study is unfeasible for the imposing requested sample size. Another interesting aspect is the low rate of mobilization failure reported. Although patients who failed a previous attempt of PBSC collection or defined as predicted poor mobilizers by the GITMO score were excluded by the study, we found nine patients (five and four in lenograstim and biosimilar filgrastim group, respectively) with a suboptimal number of peripheral CD34+ cells at peak under G-CSF (5 x 10^6-19 x 10^6/L) who could be defined as “proven poor mobilizers.” However, by using a strategy of preemptive plerixafor administration, we were able to avoid a mobilization failure in all these nine patients, which reached the CD34+ cell planned target dose in seven of nine cases (78%) and a suboptimal dose in the remaining two. Only two patients (one for each group) resulted “proven nonmobilizers” having a number of circulating CD34+ cells at peak of less than 5 x 10^6/L and failed the mobilization attempt.

In conclusion, lenograstim at conventional dosage has failed to demonstrate its superiority over biosimilar filgrastim at double the dosage at interim analysis in their first head-to-head trial. Considering that a linear increase in mobilization efficiency beyond a dosage of 5 µg/kg body weight is unlikely after chemotherapy, the hypothesis of superiority of lenograstim versus biosimilar filgrastim, even if both administered at the same conventional dosage, should be regarded as equally unlikely.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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