Biosimilar Filgrastim for Progenitor-Cell Mobilization prior to Autologous Transplantation: Retrospective Analysis of Patients with Multiple Myeloma and Lymphomas

Filgrastim Biosimilar para Mobilização de Células Progenitoras antes do Transplante Autólogo: Análise Retrospectiva de Pacientes com Mieloma Múltiplo e Linfomas

Filgrastim Biosimilar para a Movilización de Células Progenitoras antes del Trasplante Autólogo: Análisis Retrospectivo de Pacientes con Mieloma Múltiple y Linfomas

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Abstract

Introduction: Filgrastim, which plays a key role in peripheral-blood progenitor cell (PBPC) harvesting, has been available for nearly 25 years, and several filgrastim biosimilars are available. Objective: We assessed whether a biosimilar filgrastim (Filgrastine®) was associated with effective mobilization in patients undergoing PBPC harvest for autologous transplantation. Method: We reviewed the charts of patients with multiple myeloma and lymphomas treated at three institutions in Brazil. The primary outcome (mobilization success rate, MSR) was the proportion of patients in the intention-to-treat (ITT) population in whom at least 2 x 106 CD34+ cells/Kg were harvested by leukapheresis on days 5 and/or 6. The per-protocol (PP) population comprised patients who received at least 4 days of Filgrastim and had at least one CD34+ count on Days 5 or 6. Results: The daily dose of Filgrastine (on D1, with few changes thereafter) ranged from 8.5 to 28.9 mcg/Kg in the 52 patients in the ITT population, with a median of 13.8 mcg/Kg; 51 patients received at least four doses. A mean of 2.84±1.97 x 106 CD34+ cells/Kg were harvested. The MSR was 53.9% (95% CI, 39.5% to 67.8%) in the ITT population and 62.2% (95% CI, 46.5% to 76.2%) in the 45 patients in the PP population. The mobilization was considered effective by investigators in 80.8% of patients in the ITT population and 88.9% of those in the PP population. Conclusion: Despite its observational nature, this study suggests that Filgrastine® is associated with the expected success rates in PBPC harvest for autologous transplantation.

Key words: Granulocyte Colony-stimulating Factor; Filgrastim; Lymphoma; Multiple Myeloma; Peripheral Blood Stem Cell Transplantation.
INTRODUCTION

Granulocyte colony-stimulating factor (G-CSF) plays a key role in stem-cell transplantation, both for mobilization of peripheral-blood progenitor cells (PBSCs) and for hematopoietic recovery. G-CSF may be used alone, after chemotherapy, or in combination with plerixafor to mobilize PBSCs, with the choice of mobilization strategy depending in part on the underlying malignancy and on the type of transplantation. In autologous transplantation, PBPC mobilization aims to obtain the required number of cells to ensure hematopoietic recovery, with the number of leukapheresis sessions. Among the different types of G-CSF and granulocyte-macrophage CSF that have been employed, filgrastim is the one most often used.

Filgrastim has been available for nearly 25 years, and several filgrastim biosimilars (similar, but not identical, versions of the original agent for which the patent has expired) have been available since 2008 and are in clinical use in Europe and elsewhere. In the US, the first filgrastim biosimilar was approved in March 2015, and several filgrastim biosimilars are commercially available in Brazil. Despite the rigorous development and approval processes for biosimilars, concerns have been raised about the efficacy and safety of these products. Thus, it is important to assess individual products for their role in clinical practice. In the current study, we aimed at assessing a biosimilar filgrastim produced in Brazil (Filgrastine) for mobilization among patients with multiple myeloma and lymphomas undergoing PBPC harvest for autologous transplantation.

METHOD

STUDY DESIGN AND ROLE OF SPONSOR

This was a retrospective study of patients treated at three public institutions that perform bone-marrow transplantation in Brazil: Hospital das Clínicas de Ribeirão Preto (HCPRP), Hospital de Clínicas de Porto Alegre (HCPA), and the Brazilian National Cancer Institute (INCA), in Rio de Janeiro. The study protocol was approved by the Research Ethics Committees of the three participating institutions, and informed consent was waived due to its retrospective nature. The study was designed and sponsored by Blau Farmacêutica S/A, the manufacturer of the filgrastim product investigated (Filgrastine). Data analysis was conducted by a contract research organization.

ELIGIBILITY CRITERIA AND DATA COLLECTION

Eligible patients were those with multiple myeloma, non-Hodgkin lymphoma or Hodgkin lymphoma who received the specific filgrastim of interest for mobilization of PBPCs before autologous transplantation in one of the three participating institutions between January 1st, 2011, and December 31st, 2012. Patients had to be at least 18 years of age, could not have received filgrastim other than (Filgrastine), could not have received chemotherapy concurrently with filgrastim, and could not have participated in any interventional studies within 90 days from the date of the first filgrastim dose. Enrollment was done in a sequential fashion, as long as selection criteria were satisfied. Institutional medical charts were reviewed with the aim of collecting relevant data in a specific case report form. Such data included demographic, anthropometric and clinical features, prior therapies, dates, doses and route of filgrastim administration, CD34+ counts on various occasions, and whether stem-cell collection was considered successful by investigators.

OUTCOMES OF INTEREST AND POPULATIONS FOR ANALYSIS

The statistical analysis plan, finalized before database lock, specified that the primary outcome of interest was the proportion of patients in whom at least 2 x 10^6 CD34+ cells/Kg harvested after a maximum of two sessions of leukapheresis (on days 5 and/or 6 after filgrastim initiation). Secondary efficacy outcome measures were the mean number of CD34+ cells in the leukapheresis product on days 5 and/or 6; the number of days of filgrastim administration required to harvest 2 x 10^6 CD34+ cells/Kg; the proportion of patients in whom at least 5 x 10^6 CD34+ cells/Kg harvested after a maximum of two sessions of leukapheresis; and the efficacy of mobilization, as judged by investigators on the basis of successful transplantation. Safety was assessed according to adverse events considered by investigators as related to filgrastim administration during the mobilization period. Finally, the patterns of use of filgrastim were registered. The statistical analysis plan foresaw two exploratory subgroup analyses of the primary outcome, according to institution and according to underlying malignancy.

STATISTICAL ANALYSIS

Due to the retrospective nature of the study, the sample size was not calculated on the basis of statistical assumptions, but rather on practical considerations regarding a feasible enrollment. The number of patients to be enrolled by the three institutions was estimated to be between 150 and 180. In more recent randomized trials of filgrastim, with or without plerixafor, 2 x 10^6 CD34+ cells/Kg could be harvested in 88.3% of patients with multiple myeloma and 47.3% of patients with non-Hodgkin lymphomas. The enrollment 165 patients would allow detecting a rate of 67.8% (the arithmetic mean of 88.3%...
and 47.3%) for the proportion of patients in whom at least $2 \times 10^6$ CD34+ cells/Kg could be harvested after a maximum of two sessions of leukapheresis, considering a two-tailed confidence interval of 7.5% around the point estimate and a dropout rate of 10% due to missing data. Therefore, a sample size of 165 patients was within the expected range based on feasibility and would allow the detection of a clinically meaningful rate of successful mobilization.

Except for dates, there was no imputation of missing data. For dates, the 15th of the month was used when only the month and year were available for a given event. When the month was not available, the date was not used for analysis, and the same exclusion applied to variables with missing data on more than 10% of cases. All rates were computed taking as numerator the number of patients who met the outcome criteria of interest, and as the denominator the total number of patients in the population of interest. The intention-to-treat (ITT) population comprised all patients included in the study and who received at least one dose of filgrastim. The per-protocol population comprised all patients in the ITT population who received at least four days of filgrastim for mobilization and had at least one CD34+ count on Days 5 or 6. Normally distributed continuous variables were summarized by means and standard deviation (SD), whereas median and interquartile range were used for numerical variables with non-normal distribution. The unpaired t test was used to compare mean values for variables with normal distribution, while the Mann-Whitney test was used for numerical variables with non-normal distribution. Categorical variables were described by absolute and relative frequencies and 95% confidence intervals (CIs) when appropriate, and compared with Fisher’s exact or the chi-square test, as appropriate. Two-tailed significance levels of 5% were considered as indicative of statistical significance, and the analyses were performed using MedCalc (Mariakerke, Belgium, version 11).

RESULTS

PATIENT CHARACTERISTICS AND POPULATIONS FOR ANALYSIS

Patient enrolment was below expectation, due mainly to the fact that more than one filgrastim product was used at the participating institutions during the study period. As a result, only 52 patients who received Filgrastim were registered and analyzed in the ITT population. Twelve patients had no evaluation of the CD34+ cell count on D5, and 27 patients did not have the count on D6. Since seven patients did not have a CD34+ cell count either on D5 or D6, the per-protocol population consisted of 45 patients. The date of the first administration of filgrastim (D1) ranged from December 31st, 2010, to December 15th, 2012. Table 1 shows the main demographic and clinical characteristics of patients in the ITT population. Of note, information on performance status was available for 34 patients (65.4%): the performance status was 0/1/2/3/4 in 14/18/1/0/1 cases, respectively. The disease status immediately before mobilization, based on investigator opinion, was complete response in 17 patients, less than complete response in 29, progression in four, and unknown in two cases. Only 11 patients had a history of prior radiotherapy, and two had a previous autologous transplantation.

Table 1. Baseline patient characteristics (intention-to-treat population)

| Characteristic | Value or N (%) |
|----------------|----------------|
| Gender         |                |
| Female         | 24 (46.2)      |
| Male           | 28 (53.8)      |
| Age, years     |                |
| Range          | 27 to 67       |
| Mean ± SD      | 54.0 ± 9.2     |
| Median         | 56.5           |
| Race           |                |
| White          | 41 (78.9)      |
| Mulato         | 8 (15.4)       |
| Black          | 3 (5.8)        |
| Body mass index, kg/m² (N=48) |            |
| Range          | 19.9 to 44.3   |
| Mean ± SD      | 28.7 ± 6.0     |
| Malignancy, %  |                |
| Non-Hodgkin lymphoma | 3 (5.8) |   |
| Hodgkin lymphoma | 4 (7.7)      |
| Multiple myeloma | 45 (86.5)    |

EXPOSURE TO FILGRASTIM

Patient exposure to filgrastim is summarized in Table 2. The dose of filgrastim administered on D1 ranged from 8.5 to 28.9 mcg/Kg of body weight, with a mean of 15.2 mcg/Kg and a median of 13.8 mcg/Kg. The mean total dose of filgrastim on the first six days of mobilization was 86 mcg/Kg. Fifty-one patients received at least four doses of filgrastim, while one patient received only two doses (this patient underwent harvest of $10 \times 10^6$ CD34+ cells/Kg). Filgrastim was always administered subcutaneously, with the site of the first dose being the patient’s home in 38 cases, the hospital in three cases, and unknown in the
remaining 11 cases. The administered dose of filgrastim on D1 was the same as the planned dose in all cases. The administered dose of filgrastim was the same from D1 to D4 in 50 patients, while two patients had changes. Fifty patients received filgrastim on D5, and 34 received the drug on D6.

Table 2. Exposure to filgrastim

| Characteristic          | Value or N (%) |
|-------------------------|----------------|
| Doses                   | N (%)          |
| Nominal dose on D1      |                |
| 600 mcg                 | 8 (15.4)       |
| 900 mcg                 | 20 (38.5)      |
| 1,200 mcg               | 17 (32.7)      |
| 1,500 mcg               | 2 (3.9)        |
| 1,800 mcg               | 1 (1.9)        |
| 2,100 mcg               | 3 (5.8)        |
| 2,400 mcg               | 1 (1.9)        |
| Summary of D1 dose, mcg |                |
| Mean ± SD               | 1,090 ± 407    |
| Median                  | 900            |

Efficacy and Safety Outcomes

Of the 52 patients in the ITT population, 28 had at least $2 \times 10^6$ CD34+ cells/Kg harvested on D5 and/or D6. Therefore, the mobilization success rate in the ITT population was 53.9% (95% CI, 39.5% to 67.8%). All those 28 patients were part of the per-protocol population. Thus, the mobilization success rate in the per-protocol population was 62.2% (95% CI, 46.5% to 76.2%).

A mean of $2.84 \pm 1.97 \times 10^6$ CD34+ cells/Kg were harvested on D5 and/or D6. Of the 28 patients with at least $2 \times 10^6$ CD34+ cells/Kg harvested on D5 and/or D6, 14 achieved that threshold on D5, and 14 required the administration on D6 as well. The proportions of patients in whom at least $5 \times 10^6$ CD34+ cells/Kg could be harvested after a maximum of two sessions of leukapheresis were 13.5% (95% CI, 5.6% to 25.8%) in the ITT population and 15.6% (95% CI, 6.5% to 29.5%) in the per-protocol population. The mobilization was considered effective by investigators in 42 patients (80.8%) of the ITT population and 40 (88.9%) in the per-protocol population. As a result, 10 patients in the ITT population and five in the per-protocol population could not receive the planned autologous transplantation. No adverse events were reported by investigators. Seven deaths were reported and occurred between 1 and 25 months after the first day of filgrastim administration.

Exploratory Analyses

The planned subgroup analysis of the primary outcome according to institution showed nominally (but not statistically) different mobilization success rates according to institution (72.2% for HCRP, 58.8% for HCPA, and 35.7% for INCA, $P=0.277$, in the ITT population; and 81.3%, 62.5% and 38.5%, respectively, $P=0.061$, in the per-protocol population). The planned analysis according to underlying malignancy disclosed that only patients with multiple myeloma achieved the minimum threshold of $2 \times 10^6$ CD34+ cells/Kg harvested on D5 and/or D6 ($P=0.009$ in the ITT population; $P=0.010$ in the per-protocol population).

Unplanned exploratory analyses suggested no association between the primary outcome measure and gender, age or history of radiotherapy. On the other hand, there were significantly different proportions of patients with a history of radiotherapy across the three institutions: these rates were 19.0% for HCRP, 5.9% for HCPA, and 42.9% for INCA ($P=0.041$). Apparently, this imbalance was not due to underlying disease, since there were no differences in distributions of underlying disease according to center, or underlying disease according to use of radiotherapy (data not shown). The potential influence of radiotherapy on the number of CD34+ cells/Kg was also explored. Of 11 patients with previous radiotherapy, 10 had available CD34+ cell counts. Of the 41 patients without previous radiation therapy, 35 had such counts. The median number of CD34+ cells was $1.7 \times 10^6$ in patients with previous radiotherapy and $2.2 \times 10^6$ in those without such history ($P=0.133$).

Discussion

The results of this retrospective study show a success rate, defined as the collection of at least $2 \times 10^6$ CD34+ cells/Kg of body weight, with a maximum of two leukapheresis sessions, of 53.9% in the ITT population, the primary population for analysis. Although the success rate found in the ITT population is lower than the one expected at the time of the study design (67.8%), the latter figure is identical to the upper limit of the 95% CI of the success rate observed. Nevertheless, due to the absence of a statistical hypothesis to be tested, it is not possible to qualify this study as positive or negative based on formal criteria. Moreover, the success rate found on the per-protocol population was 62.2%, which is closest to the rate expected at the time of the study design. Furthermore, if a successful mobilization is considered as a relevant outcome parameter, something that was indirectly measured by assessing the opinion of the investigator, the rates found in this study were 80.8% and 88.9% in the ITT and...
per-protocol populations, respectively. It should be noted that the investigator assessment takes into account the full history of the patient, and not only the results of 2 days of leukapheresis. Moreover, it is widely recognized that nearly 20% of patients with multiple myeloma do not have a successful mobilization, regardless of the schedule of filgrastim used.  

The two chief limitations of this study are its retrospective nature and the final sample size, which was lower than expected. Despite being retrospective, the study had an approved protocol and statistical analysis plan, and data were collected with a uniform case report form. Moreover, every effort was made to collect all required data, and the analyses were performed by a third party not involved in data collection. Due to the traceability of the use of the filgrastim product of interest, something that was done using prescriptions and pharmacy records, the inclusion of patients was below expectations. This lower accrual has certainly impacted on the precision of the estimated success rates (i.e., their 95% CI). On the other hand, the possibility of bias as a result of this lower accrual cannot be ascertained, since systematic differences between patients receiving the filgrastim product of interest and other filgrastim formulations was not assessed.

The reason for the nominally lower success rate at INCA (35.7% in the ITT population), when compared with the other two institutions (72.2% and 58.8%), is not clear. It is notable, however, that the distribution of radiotherapy history differed statistically between centers, with 42.9% of patients from INCA having such history. On the other hand, the difference between the median number of CD34-positive cells in patients with and without prior radiation therapy was not statistically significant, possibly because of the small sample size. Similarly, there was no statistically significant association between a history of radiotherapy and success in mobilizing. Finally, the difference between the centers in relation to the radiation history does not seem to be due to the underlying disease. Of note, all patients treated in the center with the highest success rate (HCRP) had multiple myeloma, but the importance of this finding is uncertain. Thus, it is possible that patients in the three centers had differences in unmeasured confounders associated with a successful mobilization, such as intensity of previous treatment and disease status or bone marrow at the time of PBPC harvest.

The results of the current study can be compared with other studies that have been published. To our knowledge, no previous published study from Brazil is available for comparison. Gabús et al. reported on their experience with PBPC harvesting for autologous transplantation using another filgrastim biosimilar, Filgen JP (Clausen Filgrastim), as well as other filgrastim products available in Uruguay. While there was no difference in effectiveness between Filgen JP and other filgrastim products and the mean number of CD34+ cells harvested in that study was $4.98 \times 10^6$ CD34+ cells/Kg, which is almost twice as high as the mean found in the current study ($2.84 \times 10^6$ CD34+ cells/Kg). The reason for this difference is not clear, but Gabús et al. reported a mean filgrastim dose of 105 mcg/Kg; whereas in our study the mean total dose on the first six days of mobilization was 86 mcg/Kg, that fact that no data were collected systematically beyond D6 precludes the statement that a lower total dose of filgrastim administered to our patients underlies the differences in the mean number of CD34+ cells harvested. Higher CD34+ cell yields have been reported in other studies with biosimilar filgrastim, but whether this is due to differences in the filgrastim products, in patient profiles, different methodology for CD34+ quantification or in institution policies regarding PBPC mobilization and harvest, remains unclear.

Biosimilars offer potential benefits to patients and the healthcare system, especially because they enhance affordability and allow for increased access to expensive treatments. Some studies have shown that the use of biosimilar filgrastim offers cost savings with similar efficacy, when compared with the innovator product. These findings, alongside the apparent lack of difference in activity or safety between the innovator and biosimilar filgrastim products, support the use of biosimilar filgrastim in clinical practice.

In conclusion, despite the observational nature of this study, the results suggest that the filgrastim biosimilar of interest (Filgrastine) is effective in clinical practice, as judged by the success rates of 53.9% and 62.2% in the ITT and per-protocol populations, and the rates of success as assessed by investigators (80.8% and 88.9%, respectively). Ideally, these findings should be confirmed by a comparative clinical trial.

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AUTHOR CONTRIBUTIONS

All authors worked on the design and planning of the research project, obtaining and/or analyzing data, as well as writing and reviewing the manuscript.
CONFLICT OF INTEREST STATEMENT

Nothing to Declare.

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