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Tbo-Filgrastim versus Filgrastim during Mobilization and Neutrophil Engraftment for Autologous Stem Cell Transplantation

Mohammed M. Elayan [1,*], Justin G. Horowitz [1,2], Jose M. Magraner [1], Paul J. Shaughnessy [1,3], Carlos Bachier [1,3]

[1] *Adult Blood and Marrow Transplant, Texas Transplant Institute, San Antonio, Texas*
[2] *University of Texas College of Pharmacy, Austin, Texas*
[3] *Sarah Cannon Blood Cancer Network, Nashville, Tennessee*

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A B S T R A C T

There are limited data available supporting the use of the recombinant granulocyte colony–stimulating factor (G-CSF), tbo-filgrastim, rather than traditionally used filgrastim to mobilize peripheral blood stem cells (PBSC) or to accelerate engraftment after autologous stem cell transplantation (ASCT). We sought to compare the efficacy and cost of tbo-filgrastim to filgrastim in these settings. Patients diagnosed with lymphoma or plasma cell disorders undergoing G-CSF mobilization, with or without plerixafor, were included in this retrospective analysis. The primary outcome was total collected $CD34^+$ cells/kg. Secondary mobilization endpoints included peripheral $CD34^+$ cells/μL on days 4 and 5 of mobilization, adjunctive use of plerixafor, $CD34^+$ cells/kg collected on day 5, number of collection days and volumes processed, number of collections reaching 5 million $CD34^+$ cells/kg, and percent reaching target collection goal in 1 day. Secondary engraftment endpoints included time to neutrophil and platelet engraftment, number of blood product transfusions required before engraftment, events of febrile neutropenia, and length of stay. A total of 185 patients were included in the final analysis. Patients receiving filgrastim ($n = 86$) collected a median of 5.56×10^6 $CD34^+$ cells/kg, compared with a median of 5.85×10^6 $CD34^+$ cells/kg in the tbo-filgrastim group ($n = 99$; $P = .58$). There were no statistically significant differences in all secondary endpoints with the exception of apheresis volumes processed (tbo-filgrastim, 17.0 liters versus filgrastim, 19.7 liters; $P < .01$) and mean platelet transfusions (tbo-filgrastim, 1.7 units versus filgrastim, 1.4 units; $P = .04$). In conclusion, tbo-filgrastim demonstrated similar $CD34^+$ yield compared with filgrastim in mobilization and post-transplantation settings, with no clinically meaningful differences in secondary efficacy and safety endpoints. Furthermore, tbo-filgrastim utilization was associated with cost savings of approximately $1406 per patient utilizing average wholesale price.

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INTRODUCTION

High-dose chemotherapy followed by autologous stem cell transplantation (ASCT) remains a viable treatment option for several hematological malignancies [1-3]. Various strategies for collection of peripheral blood stem cells (PBSC) have been employed, including chemomobilization and utilization of recombinant granulocyte colony–stimulating factor (G-CSF), which is widely used because of its efficacy, safety, and cost [4-17]. The American Society for Blood and Marrow Transplantation mobilization guidelines outline evidence supporting these approaches in detail [18]. Although the guidelines' authors recognize the potential contribution of biosimilars in PBSC mobilization, additional studies were recommended. Limited reports demonstrate equivalence utilizing biosimilars in the mobilization and post-transplantation setting; however, no consistent evidence to guide definitive practice changes has emerged [19-27].

Filgrastim, the most utilized recombinant G-CSF in the United States, is approved by the Food and Drug Administration (FDA) for multiple indications, including PBSC

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* Correspondence and reprint requests: Mohammed M. Elayan, Texas Transplant Institute, Methodist Hospital, Adult Blood and Marrow Transplant, 4410 Medical Drive, Suite 410, San Antonio, TX 78229.
E-mail address: mohammed.elayan@mhshealth.com (M.M. Elayan).

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mobilization and to improve time to neutrophil engraftment after hematopoietic stem cell transplantation [28]. Because of the lack of an FDA biosimilar approval pathway at the time of submission, tbo-filgrastim was studied and approved through an original biologics license application as a separate entity [29]. Therefore, tbo-filgrastim does not carry similar indications to filgrastim despite similarities in structure, formulation, and mechanism [30].

Current literature confirms bioequivalent activity of tbo-filgrastim to filgrastim in the prophylaxis and treatment of febrile neutropenia in patients receiving myelosuppressive chemotherapy for nonmyeloid malignancies [31-33]. Phase I studies validated that tbo-filgrastim maintains a similar pharmacokinetic profile to filgrastim, and pharmacodynamic studies demonstrated sufficient mobilization of $CD34^+$ cells [34,35]. Comparison of these 2 agents in this setting is of particular interest because of the reduced costs of tbo-filgrastim compared with filgrastim. Therefore, this study sought to compare and describe outcomes related to mobilization and engraftment utilizing tbo-filgrastim to those outcomes after using conventional filgrastim in the setting of ASCT. Additionally, the financial impact of tbo-filgrastim utilization during PBSC collection and neutrophil engraftment after transplantation were evaluated.

METHODS

This institutional review board–approved study is a retrospective data review of patients undergoing PBSC collection and ASCT at the Texas Transplant Institute from June 2013 to December 2014. Patients were identified through electronic medical records and pharmacy database systems. Successive ASCT recipients utilizing G-CSF product for PBSC mobilization and neutrophil engraftment from this time period were selected for analysis. Patients were included in the final data analysis if they were at least 18 years of age and diagnosed with lymphoma or a plasma cell disorder, such as multiple myeloma, amyloidosis, or Waldenstrom's macroglobulinemia. Patients receiving a second transplantation or chemotherapy mobilization of PBSC were excluded. Additionally, patients lacking complete documentation or inappropriate G-CSF administration were not included in the final analysis.

Stem cells were mobilized utilizing our institutional guidelines, which remained constant throughout the study duration. G-CSF was administered at a dose of 10 μg/kg, rounded to nearest vial size, daily for 4 days before PBSC collection on day 5. The adjunct use of plerixafor was determined by circulating $CD34^+$ cells/μL on day 4 of mobilization. If circulating $CD34^+$ cell count was ≤10 cells/μL and 1 transplantation was planned, plerixafor was administered at a dose of 24 mg with G-CSF daily until $\geq 2 \times 10^6$ $CD34^+$ cells/kg were collected. If 2 transplantations were planned and circulating $CD34^+$ cell count was ≤20 cells/μL, plerixafor and G-CSF were administered as previously described until $\geq 4 \times 10^6$ $CD34^+$ cells/kg were collected. After transplantation, G-CSF was administered at a dose of 5 μg/kg daily beginning on day +7 and continued until neutrophil engraftment. Filgrastim was replaced with tbo-filgrastim in the institutional formulary in January 2014, from which point on all patients received tbo-filgrastim for mobilization and engraftment. Patients were apheresed utilizing the COBE Spectra Apheresis System (Terumo BCT, Lakewood, CO), Spectra Optia Apheresis system (Terumo BCT, Lakewood, CO), or the Fresenius AS104 (Fresenius, Concord, CA).

The primary objective of this study was to compare total collected $CD34^+$ cells/kg between tbo-filgrastim and filgrastim groups. Secondary endpoints included examining efficacy, safety, and cost outcomes. For mobilization, we compared peripheral $CD34^+$ cells/μL on days 4 and 5 of mobilization, adjunctive use of plerixafor, $CD34^+$ cells/kg collected on day 5, number of collection days and volumes processed, total number of $CD34^+$ cells/kg collected, number of collections reaching 5 million CD34+ cells/kg, and percent reaching target collection goal in 1 day. Engraftment outcomes included days until neutrophil and platelet engraftment, defined as an absolute neutrophil count ≥ 500 cells/mm^3 and a platelet count ≥ 20,000/μL, respectively. Post-transplantation safety outcomes included events of febrile neutropenia, classified as a temperature of ≥100.4°F before neutrophil engraftment, transfusion of packed red blood cells and platelets, and length of stay. All patients received standardized supportive care including prophylactic antibiotics beginning day -1 and transfusions of leuko-reduced, irradiated blood products. Packed red blood cells were given as needed for hemoglobin ≤ 8.5 g/dL and platelets were transfused for platelet counts ≤ 10,000/μL. Cost minimization outcomes were analyzed using the value of both products according to average wholesale price at the time of G-CSF administration. Utilization was determined based on total G-CSF use.

Statistical analysis was performed using JMP Version 12 (SAS Institute Inc., Cary, NC). Data with a normal distribution was analyzed using Student's *t*-test, and the Wilcoxon-Mann-Whitney test was utilized for nonparametric data. Comparisons with a P value of $< .05$ were considered statistically significant.

RESULTS

A total of 222 patients receiving an ASCT during the study time period were identified. Of those, 185 met inclusion criteria for analysis (Figure 1). Demographic information is described in Table 1. Patients were excluded for receiving prior ASCT (n = 20), receiving chemo-mobilization (n = 13), or having incomplete documentation of study endpoints (n = 4). Within the study population, median patient age was 60 years (range, 21 to 82), 106 (57%) were male, and 86 (46%) received filgrastim. The median age of patients in the filgrastim group was higher than those receiving tbo-filgrastim (61.5 versus 57.0 years, $P < .01$). Among patients with plasma cell disorders receiving filgrastim, 87% were in partial remission or had stable disease at time of mobilization and transplantation compared with 65% in the tbo-filgrastim group ($P = .03$). All other demographic characteristics were similar. With the exception of 1 patient who received busulfan plus melphalan, all patients with plasma cell disorders received conditioning with high-dose melphalan. All patients with lymphoma received carmustine, etoposide, cytarabine, melphalan, with or without rituximab conditioning.

For the primary objective, we evaluated the total $CD34^+$ cells/kg collected during PBSC mobilization. Patients receiving tbo-filgrastim collected a median of 5.85×10^6 $CD34^+$ cells/kg (range, .12 to 19.83) compared with 5.56×10^6 $CD34^+$ cells/kg (range, 1.69 to 16.34) for the filgrastim group ($P = .58$).

PBSC mobilization and collection secondary endpoints did not differ between the 2 groups with the exception of apheresis equipment utilized and processing volumes (Table 2). The majority of patients in the filgrastim group (85%) underwent collection using the COBE Spectra (Terumo BCT) and over one half of the tbo-filgrastim group underwent

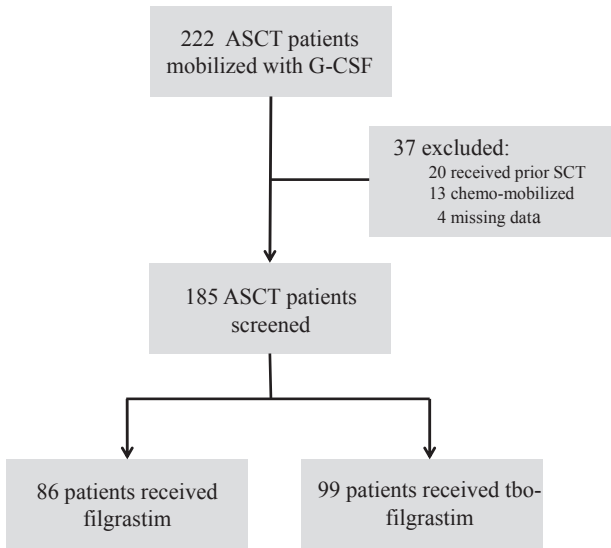

Figure 1. Patient flow chart.

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