The effects of single-dose biosimilar filgrastim (leucostim®), filgrastim (neupogen®) and lenograstim (granocyte®) on bone marrow-derived stem cell collection for allogeneic stem cell transplantation: A single center experience and systematic review

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Abstract

Introduction: Bone marrow (BM) has been used as the source of stem cells for allogeneic hematopoietic stem cell transplant. However, peripheral blood stem cells (PBSC) for allogeneic HSCT have gained more popularity after the recent use of granulocyte colony-stimulating factor (G-CSF) for mobilization. Adult studies of the BM product mobilized using G-CSF (G-BM) have shown faster white blood cell engraftment, similar to that produced by PBSC, however, with less acute and chronic graft versus host disease disease. Methods: In order to increase the CD34 cell content of the bone marrow product, three different G-CSFs were used: biosimilar filgrastim (Leucostim®) (n=29), original filgrastim (Neupogen®) (n=30), and lenograstim (Granocyte®) (n=30). These G-CSFs were compared with one another and with the control group (n=30). The data obtained with the products collected from the BM of healthy donors in the control group and those who received G-CSF were analyzed. All donors were administered G-CSF 10 μg/kg daily at least 24 hours before BM harvesting. Results: In terms of the amount of CD34/UL per microliter BM harvesting, the group receiving Lenograstim (Granocyte®) was found to have a statistically significant higher CD34/UL value compared to the other groups. There was no statistically significant difference between the median CD34/UL values across the control, filgrastim and biosimilar-filgrastim groups. Biosimilar filgrastim (Leucostim®), original filgrastim (Neupogen®) and lenograstim (Granocyte®) can be safely used for BM CD34 cell mobilization in donors of patients undergoing allo-HSCT. Conclusion: Considering the amount of CD34/UL collected in the product, Lenograstim (Granocyte®) should be more preferable.

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) provides a potentially curative treatment for both malignant and non-malignant hematopoietic diseases in pediatric and adult age groups.[1] While bone marrow (BM) has been the most common source of both autologous and allogeneic hematopoietic stem cells for many years, peripheral blood stem cells (PBSC) mobilized by the growth factor, granulocyte colony stimulating factor (G-CSF) have become a more important source for hematopoietic stem cells in recent years. Early clinical studies on the source of stem cells showed that PBSC provided a higher dose of stem cells as well as faster engraftment benefit compared to BM without G-CSF modification.[2]Post-transplantation engraftment is directly related to the source of hematopoietic stem cells and the number of immature progenitor cells in the graft.[3]

Despite being the recently preferred source of stem cells for most adults with a transplant from an HLA-

matched sibling donor, PBSC appears to be less commonly preferred as a standard stem cell source for pediatric patients. A recent analysis conducted by the International Bone Marrow Transplant Registry (IBMTR) showed that the use of PBSC in pediatric patients had a higher risk of chronic graft versus host disease (GvHD) and transplantation-related mortality. In addition, apheresis often requires insertion of a central venous catheter, which challenges the feasibility in children. [2] On the other hand, PBSC has recently been the preferred source for allogeneic HSCT in adults, especially in those with malignant disease.[2,3,4] As a result of BMSC being more widely preferred as a stem cell source for allogeneic HSCT during childhood, acute and chronic GvHD, which are among the most important problems increasing transplant-related mortality (TRM), are less common compared to adults.[5]

While G-CSF administration to autologous transplant donors in order to collect PBSC for autologous transplantation is now routinely used, recently, it has also been frequently used in normal healthy donors for allogeneic transplantation.[1] Results from studies on different donor-derived stem cells in allogeneic HSCT have shown that higher doses of BM nucleated cell doses given to HSCT recipients result in faster engraftment and improved survival.[6]

It has been shown in numerous studies that the collection of CD34 cells from PBSC and BMSC after administering growth factors such as G-CSF to donors, accelerates engraftment with the quantitative and qualitative effects of growth factors on progenitor cells and increases the number of nucleated and CD34 cells for harvesting.[7] When G-CSF is used to collect stem cells from a healthy donor whose stem cell source is BM, the number of nucleated and CD34 cells collected in the BM product increases and faster engraftment occurs without increasing the risk of GvHD. [7,8]

The present study reports the results we obtained by administering a single dose of 3 different G-CSF molecules to healthy donors before collecting CD34 cells from BM.

Methods

Our Pediatric Hematology-Oncology and Stem Cell Transplantation Center has a comprehensive and large database of all patients and donors. In this center, transplantations were performed using the BM product obtained by administering G-CSF to healthy donors in order to increase the number of collected total nucleated cells (TNC) and CD34 cells for some patients. The data obtained with the products collected from the BM of healthy donors after G-CSF administration were analyzed in detail. Three different products were used as G-CSF: biosimilar filgrastim (Leucostim®) (n=29), original filgrastim (Neupogen®) (n=30), and lenograstim (Granocyte®) (n=30). These G-CSFs were compared with one another and with the control group (n=30). All donors were treated with a standard institutional protocol. Approval for the study was obtained from our local institutional review board.

BM priming and collection

All donors received G-CSF 10 μg/kg daily as a single subcutaneous injection at least 24 hours before BM harvesting (Day -1). In addition, hemogram was checked using a peripheral blood sample before G-CSF was administered to all donors. At 24 hours, immediately before collecting the BM product, another hemogram was measured from a peripheral blood sample. The patients in the control group were not administered with any G-CSF. On Day 0, BM was collected from both posterior iliac bones under general anesthesia in line with the standard training procedures, aiming a target volume of 10-20 mL per kg body weight of the recipient and not exceeding 20 mL per kg body weight of the donor. BM was collected by volume and mid-collection cell counts were not performed. HSC collection was performed in a single session for all patients. All donors were fully assessed for any events related to G-CSF use or BM harvesting prior to donation, on G-CSF administration days and after BM harvesting until discharge from hospital.

Evaluations and definitions

BM products were analyzed by flow cytometry for CD34+, T-cell cytotoxic (CD8/UL), T-cell helper (CD4/UL), B-cell (CD19/UL) and NK cell (CD16/UL) subsets using previously published methods. The cell subsets, WBC-1 %, PNL-1 %, LYM-1 %, MON-1 %, EOS-1 %, and BASO-1 %, were analyzed in a

peripheral blood sample before G-CSF administration. The same procedure was performed after G-CSF administration, where the cell subsets, WBC-2 %, PNL-2 %, LYM-2 %, MON-2 %, EOS-2 %, and BASO-2 % were re-analyzed.

Cell counts

Total nucleated counts were obtained using an automated Navios EX Flow Cytometer and Kaluza Analysis Software (Beckman Coulter Inc., Miami, FL, USA). Flow cytometry analysis was performed using appropriate monoclonal antibodies that recognize CD45+ (KrO), CD3+(FITC), CD34+(PE), CD8+ (PC7), CD4+ (PC5.5), CD19 (ECD) and CD16+ (PE) cells (Beckman Coulter Inc., Marseille, France). The number of CD34+ cells infused was calculated as the % of antigens and a FAC Sort instrument from CD34+/CD45+ cells × the total nucleated count.

Donor tolerance for the mobilization regimen

The mobilization regimen was completed by administering different G-CSF products as a single dose to all donors before stem cells were collected from BM. None of the donors reported diffuse bone pain after harvesting; only moderate pain localized to the BM aspiration area was reported. None of the donors required acetaminophen for pain.

Statistical Analysis

Statistical analyses were performed using the IBM SPSS software (version 20, SPSS, Inc., Chicago, USA). Data with non-normal distribution were expressed as median in the comparison using the Mann-Whitney test. The chi-square test or Fisher's exact test was used to compare the differences between groups of categorical data. $P < 0.05$ was considered significant.

Results

Study population

A total of 119 healthy donors were included in this study. All cases were stratified into 4 different groups, including a control group. The control group consisted of 30 donors. The donors, except those in the control group, received 3 different G-CSFs, i.e. biosimilar filgrastim (Leucostim®) (n=29), original filgrastim (Neupogen®) (n=30), and lenograstim (Granocyte®) (n=30) by subcutaneous administration 24 hours before the BM product was collected. Median age of the donors participating in the study was 13 (1-55) years and 51.3% (61 patients) were female. There was no statistically significant difference between the drug groups and demographic variables. (Table 1)

There was no statistically significant difference between the initial hemogram measurements of the donors across the groups, including the control group. However, in the hemogram measurements obtained immediately before collecting the BM product at 24 hours after G-CSF administration, a statistically significant difference was noted between the groups in WBC-2, PNL-2, and BASO-2 measurements.

The median WBC-2 value of the control group was statistically significantly lower than the other groups, while the median WBC value of the group receiving lenograstim (Granocyte®) was statistically significantly higher than the other groups, and there was no difference in terms of WBC-2 between the healthy donors who received biosimilar filgrastim (Leucostim®) and the original filgrastim (Neupogen®) product. There was no statistically significant difference in median PNL-2 values among the treated (G-CSF) donor groups. In addition, the median BASO-2 value was found to be higher in the control group than the groups that received G-CSF. When the first and second hemogram measurements of the donors receiving G-CSF were evaluated, a statistically significant change was found in all groups (Table 2).

There was no statistically significant difference between the groups in terms of WBC count of the product collected from the bone marrow. However, there was a statistically significant difference between the groups in terms of CD34/UL amount per microliter in the product. When the reason for the difference in CD34/UL was investigated, it was determined that the group receiving lenograstim (Granocyte®) had a statistically

significantly higher CD34/UL value compared to the other groups. On the other hand, no statistically significant difference was found in terms of median CD34/UL values between the control group and the groups that received biosimilar filgrastim (Leucostim®) or original filgrastim (Neupogen®) (Table 3).

When the collected bone marrow product was assessed in terms of cell subgroups [CD34, T-cell cytotoxic (CD8/UL), T-cell helper (CD4/UL), B-cell (CD19/UL) and NK cell (CD16/UL)], a statistically significant difference was found only in terms of B cells between the control group and the group receiving original filgrastim (Neupogen®) (p=0.003).

Discussion

The concept of biosimilar products essentially refers to copies of biologic products whose patent protection has expired. Given the complexity of manufacturing biologics, these products are obtained differently from generics (copies of small-molecule drugs) through a specific regulatory process. In this context, obtaining a biosimilar status requires evidence of physico-chemical, pharmacological and clinical similarity, including comparative trials for at least one "sensitive" indication for which the reference product is licensed. The most important benefits of biosimilars include reduced healthcare expenditures and ease of access.[9]

G-CSF is primarily produced by fibroblasts, bone marrow endothelial cells, monocytes and macrophages. G-CSF exerts its main effect by ensuring the production, maturation, mobilization and survival of neutrophils.[10] It also plays a role in chemotaxis by stimulating the release of arachidonic acid from neutrophils, production of leukocyte alkaline phosphatase (LAP), myeloperoxidase, and superoxide anions.[11] In addition to being used to prevent or shorten the duration of severe neutropenia after chemotherapy, especially in the pediatric age group, G-CSF is also commonly used for stem cell mobilization. Currently, while PBSC mobilized with G-CSF is widely used as a stem cell source, stem cells are rarely obtained from BM, and G-CSF is rarely used to provide mobilization in this setting.[12]

Although PBSC is the more commonly preferred source of stem cells for adult patients, BM remains the main stem cell source for standard allogeneic HSCT performed in children due to a variety of conditions, including certain malignancies, hemoglobinopathies, bone marrow failure syndromes, immunodeficiency, and congenital metabolic diseases.[13]

Compared to BM, a PBSC graft contains roughly 3-10 times as many CD34+ and CD3+ cells. Preparation by using G-CSF for stem cell collection from BM substantially alters the growth and proliferative properties of the bone marrow cells. After G-CSF stimulation to healthy donors, the number of CD34+ cells increase by 26-fold on average in peripheral blood, while this increase is only 1.4-1.7-fold in the bone marrow. These results suggest that G-BM stem cells may acquire proliferative properties leading to a faster hematopoietic recovery after HSCT. Furthermore, modulating the expression of certain adhesion molecules involved in the pathogenesis of GvHD, such as VLA-4, ICAM-1, L-selectin, and LFA-1 as well as the migration and homing of T-cells, significantly reduces the development of GvHD in G-BM. Selective inhibition of these adhesion molecules may explain the reduced incidence of GvHD after G-BM transplantation.[14]

The objective of G-BM transplantation is to ensure faster engraftment without increasing the risk of GvHD and allow the patient's recovery in a shorter period of time. When the outcomes in patients receiving G-BM are compared to historic records or case-control cohort studies of patients receiving BM only, study results reveal that G-BM patients achieve higher numbers of total nucleated cells, CD34+ cells, CFU-GM, and faster neutrophil and platelet engraftment. [7,15]

BM prepared with G-CSF is an alternative stem cell source that can provide a higher number of stem cells without increasing the risk of GvHD. Kim et. al. reported faster engraftment in their study including 33 patients who underwent G-BM transplantation (median time: 13 days for neutrophils and 18 days for platelets) as well as a lower incidence of acute GvHD (> grade II, 12%) and chronic GvHD (34%), and the cumulative incidence of TRM was 15%. The probability of 10-year overall and event-free survival (EFS) was 68% and 62%, respectively.[16] Similarly, Isola et. al. observed faster neutrophil and platelet engraftment in 10 patients who received G-CSF 10 g/kg two days before allogeneic BM harvesting compared to the control

group who underwent BM transplantation without G-CSF.[15]

In a prospective randomized study comparing G-CSF-stimulated BM and PBSC in adult patients with malignant disease, there was no significant difference in the duration of neutrophil and platelet engraftment, but when compared in terms of GvHD risk, PBSC recipients had a much higher risk of acute (17% vs. 46%) and chronic (27% vs. 77%) GvHD.[3]

While the ideal G-CSF dose for PBSC is well-established in studies, the ideal G-CSF dose for preparation before BM harvesting appears to be less understood. A prospective multicenter study in children who received allogeneic BM from HLA-identical siblings showed that G-CSF administration in the pediatric age group was well tolerated and resulted in a high dose of nucleated and CD34+ cells after using G-CSF at a dose of 5 μg/kg for five days.[2,3]

In a single-center study of a small number of pediatric patients, the investigators used a dose of 5 μg/kg for three days before BM harvesting and compared the results with similar patients who did not receive G-CSF stimulation. Patients who received G-CSF prior to BM harvesting had higher doses of TNC and CD34+ cells; however, faster engraftment was not achieved although all patients received post-transplant G-CSF. In a different prospective study involving 57 patients, after receiving 10 μg/kg of G-CSF daily for 5 days, patients were randomized to G-CSF-stimulated BM (28 patients) and G-CSF-stimulated PBSC (G-PBSC) (29 patients). Patients in the G-PBSC group received three-fold CD34+ cells and nine-fold CD3+ cells than the patients in the G-BM group. Median times to neutrophil and platelet engraftment were similar. The cumulative incidences of refractory aGvHD and extensive cGvHD were significantly higher for the G-PB group. It was concluded by the authors that G-BM results in less severe aGvHD and less cGvHD compared to G-PB graft. Post-transplant recurrence rate and OS were similar.[8] A comprehensive review of the literature shows numerous studies demonstrating that the use of BM prepared with G-CSF provides faster neutrophil and platelet engraftment in recipients, with lower rates of GvHD and TRM.

There are many studies of PBSC that involve different G-CSF products applied for stem cell mobilization in HSCT and compare the results obtained with these products. Similarly, while there are studies that compare the doses of G-CSF used for cell mobilization from BM or test whether this approach should be adopted, there is no study comparing different G-CSF products administered and investigating the effect of G-CSF products on the collected BM product. When we evaluated the results of our patients in light of the available information, we found that lenograstim, which was administered as a single dose 24 hours before transplantation, resulted in obtaining a higher level of CD34/UL compared to the control group and the groups that received filgrastim or biosimilar filgrastim. In a PBSC study which compared lenograstim, filgrastim and biosimilar filgrastim, similar to our study, no difference was found in terms of CD34/UL. However, the target CD34 cell count was reached with an apheresis procedure in 87% of the donors receiving lenograstim and 93% of the donors receiving biosimilar filgrastim. [17] In a different multicenter study involving a large number of adult patients who underwent autologous transplantation, lenograstim, filgrastim and biosimilar filgrastim were compared, and no difference was found between the groups in terms of CD34+ progenitor cells (×106/kg). [18] In another study involving 243 cases of allogeneic PBSC by Sivgin et al., no difference was found in terms of CD34/UL obtained from healthy donors using lenograstim, filgrastim or biosimilar filgrastim, and biosimilar filgrastim (Leucostim®) was found to be comparable with original Filgrastim (Neupogen®) and lenograstim (Granocyte®) for PBSC mobilization in donors of patients undergoing allo-HSCT.[19]

The limitation of our study is that it was not conducted with a large number of subjects in the donor and control groups, especially in the pediatric age group. We acknowledge that the content of the post-transplantation product should have been evaluated in a high number of donors and included in this study. We also believe the late effects of biosimilar filgrastim (Leucostim®), original filgrastim (Neupogen®) and lenograstim (Granocyte®) should be evaluated. The strength of our study is that it is the first to use different G-CSF molecules for the mobilization of stem cells from the bone marrow, and the first to compare the results of different G-CSFs with one another as well as with a control group.

In conclusion, biosimilar filgrastim (Leucostim®), original filgrastim (Neupogen®) and lenograstim (Granocyte®) can be safely used for BM mobilization in donors of patients undergoing allo-HSCT. However, lenograstim (Granocyte®) should be preferred with regard to median CD34/UL count. Further studies are required to determine the ideal dose and number of administrations in this setting. Our results warrant being supported by prospective studies with larger case series.

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LEGENDS

TABLE 1 Demographic Variables

TABLE 2 Data for PBSC collection.

TABLE 3 Assessment of cell subgroups within the bone marrow product.

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