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Mobilization of Hematopoietic Stem Cells with Lenograstim in Healthy Donors: Efficacy and Safety Analysis According to Donor Age

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We reviewed and analyzed safety and efficacy data after mobilization with granulocyte colony-stimulating factor (G-CSF) according to healthy donor's (HDs) age as follows: <50 years (HDs-1, n = 161), aged 50 to 59 years (HDs-2, n = 62), and ≥60 years or over (HDs-3, n = 23). Two hundred forty-six HDs were evaluated, and their characteristics were well balanced among age groups: most were male, siblings, and HLA matched. According to age group, the median numbers of $CD34^+$ cells in the peripheral blood for HDs-1, HDs-2, and HDs-3 were, respectively, 44.5, 34.5, and 26 (HDs-1 versus HDs-2, $P = .002$; HDs-1 versus HDs-3, $P = .036$; HDs-2 versus HDs-3, $P =$ n.s.) at day 4 and 65.5, 58, and 46 (HDs-1 versus HDs-2, $P = .039$; HDs-1 versus HDs-3, $P = .002$; HDs-2 versus HDs-3, $P =$ n.s.) at day 5. With a median apheresis session of 1, the number of $CD34^+$ cells/kg recipient body weight collected was not significantly different (6.4 in HDs-1, 6.0 in HDs-2, and 5.7 in HDs-3, $P =$ n.s.). Short- and long-term safety did not differ among age groups. Bone pain was reported as the most frequent short-term adverse event (76.5%). After a median follow-up of 7.8 years, the observed rate of solid tumors, hematological malignancies, and cardiovascular and autoimmune events was similar to the expected incidence for these diseases in Western countries. These results show that G-CSF is effective in the mobilization of older HDs. Moreover, our data contribute to the growing body of evidence in support of the long-term safety of G-CSF for allogeneic donor stem cell mobilization also for elderly HDs.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an established procedure for many malignancies of the hematopoietic system [1]. Over the past 15 to 20 years, the landscape of allografting has changed, from being rarely performed in patients ≥50 years to accounting for a little less than half of the transplantations reported [1,2]. The reason for the rise in HSCT among old adults ranges from the introduction of lower toxicity conditioning regimens to the increase in the number of "fit" older patients requiring chemotherapy [3-5].

Older patients on average have older siblings who could be considered as donors [4]; in some cases these siblings could be the only option for patients to undergo allo-HSCT [2]. Very few matched unrelated donors (MUDs) are over age 50 years, and an open question is the optimal choice between a young MUD or an older matched sibling, if they are both available [4]. Matched sibling donors were shown to provide improved overall survival and reduced acute graft-versus-host disease (GVHD) relative to MUDs [6]. Other studies show similar outcomes after matched sibling donors compared with MUD among older patients [7].

In healthy donors (HDs), stem cells can be collected in 2 ways: bone marrow (BM) harvest or collection from

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peripheral blood (PBSC) by apheresis [8]. BM harvest is performed under general or regional anesthesia [9], and stem cells are directly aspirated from both hip bones (posterior superior iliac crests). The complications of BM harvesting are well known and are usually mild and self-limiting. Severe side effects, such as infections, anesthetic complications, and bleeding, have been described but are rare [10-12]. PBSC collection involves administering subcutaneous injections of granulocyte colony-stimulating factor (G-CSF) to the donor for approximately 4 to 5 days. The avoidance of anesthesia, blood transfusion, and prolonged pain are potential benefits of PBSC donation [13]. The choice of stem cell source is determined by donor preference, recipient diagnosis, disease stage, age, intended conditioning regimen, and other factors that may contribute to transplant-related mortality [14].

A systematic review showed that overall survival after allo-HSCT using PBSC was similar to using BM in adults with hematological malignancies. The authors found moderate evidence that PBSC transplantation was associated with faster engraftment of neutrophils and platelets, but a higher risk of GVHD, in terms of more overall and extensive chronic GVHD [15]. Kollman et al. [16] showed the use of younger donors may lower the incidence of GVHD and improve survival after BM transplantation, whereas Richa et al. [6] demonstrated that older donor age has no detrimental effect on graft function or transplant outcome after PBSC allo-HSCT.

A donor of advance d age who meets the requirements of the mobilization procedure may be considered. Some studies indicate that older age correlates with mobilizing fewer $CD34^+$ cells in the peripheral blood and therefore lower $CD34^+$ cell yields [17-20]. Comorbidities do not reduce the capacity to mobilize $CD34^+$ cells, and medically cleared older sibling donors aged 50 to 70 years generally have adequate PBSC $CD34^+$ cells for transplantation [20,21].

Although analyses comparing BM with PBSC donation have generally demonstrated differences in adverse event profiles with similar overall effects [21], few data are available to assess the efficacy and short- and long-term safety of G-CSF mobilization in an older HD population [13,22-27]. The aim of the present single-institution study was to assess the safety and efficacy of the mobilization of PBSC in older HDs treated with G-CSF.

METHODS

From 1997 to 2013, 246 consecutive HDs were referred to our transplant unit to undergo mobilization and apheresis of PBSC for related allo-HSCT. For this retrospective study, donors were divided into 3 groups according to age: HDs-1, patients <age 50 years; HDs-2, patients aged 50 to 59 years; and HDs-3, patients aged ≥60. Demographic, mobilization, and apheresis characteristics from all donors were collected.

Donor evaluation comprised the following elements: (1) detailed medical history, (2) physical assessment with special consideration of peripheral veins, (3) electrocardiogram at rest and echocardiography, (4) ultrasound examination of the upper abdomen with measurement of spleen diameter, and (5) laboratory examinations including complete blood count with differential, clinical chemistry, urinalysis, infectious disease markers, ABO, rhesus (Rh) typing, and pregnancy test in women of childbearing age (urine or serum). Thrombophilia screening comprised testing for protein C, protein S, factor VIII, and homocysteine plasmatic levels; antithrombin III activity; and acquired activated protein C resistance.

To collect PBSCs, donors had to meet the following criteria: (1) not on treatment with acetylsalicylic acid or antiaggregates, anticoagulants, angiotensin-converting enzyme inhibitors, or lithium; (2) no splenomegaly; (3) negative personal history of coagulation disorders or history of iritis, episcleritis, or active autoimmune diseases; (4) no chronic cardiovascular and respiratory disease; (5) not a carrier of the sickle cell trait; (6) able to provide peripheral venous access; and (7) not currently pregnant or breastfeeding. Written informed consent of donors was obtained after a detailed description of the potential side effects and risks of G-CSF mobilization and apheresis compared with BM donation with general anesthesia.

Mobilization and Apheresis

Donors were mobilized with G-CSF (ie, lenograstim) with subcutaneous doses of 10 μg/kg either as a single or split dose. The day of pretreatment evaluation and the first day of lenograstim administration were conventionally considered as day 0 and day 1, respectively. Prophylaxis with paracetamol was administered to prevent the potential side effects of lenograstim.

$CD34^+$ cell measurements in peripheral blood were performed during mobilization with the International Society of Hematotherapy and Graft Engineering (ISHAGE) single-platform method in all groups of HDs [28,29]. $CD34^+$ cells were monitored on day 4 and daily thereafter until the completion of apheresis. The collection of PBSCs was performed after lenograstim stimulation using identical procedures in all donors on day 5. The target PBSC dose to be collected was $\geq 4 \times 10^6$ $CD34^+$ cells/kg recipient body weight, whereas a minimal cell dose of $\geq 2 \times 10^6$ $CD34^+$ cells/kg was accepted.

Apheresis was performed daily until the target dose was reached. PBSCs were collected 1 to 2 hours after the last dose of lenograstim. Apheresis was carried out with continuous-flow apheresis equipment (COM.TEC cell separators, AS 104/AS 204, and COM.TEC in; Fresenius Hemo-Care GmbH, Bad Homburg, Germany) through bilateral peripheral venous access, using citrate-dextrose as the anticoagulant. Lenograstim was continued until the completion of stem cell collection provided that WBC count did not exceed 60×10^9/L. Apheresis was not performed in donors who showed a platelet count lower than 75×10^9/L.

Efficacy Endpoints

The primary endpoints were to evaluate the peak $CD34^+$ cell count in peripheral blood at days 4 and 5 during mobilization with lenograstim and the total number of $CD34^+$ cells per recipient and donor body weight collected. Secondary endpoints were percentage of donors achieving $\geq 2 \times 10^6$ and $\geq 4 \times 10^6$ $CD34^+$ cells/kg recipient and percentage of those achieving the same targets with a single apheresis, median number of WBCs at days 4 and 5, and mobilization failure rate. Mobilization failure was defined as a collection of $CD34^+$ cells $< 2 \times 10^6$/kg recipient. As an efficacy evaluation, we analyzed the success of HSC engraftment in patients and the percentage of patient treatment-related mortality, defined as any death related to a fatal complication in the absence of the underlying disease within 100 days of transplantation.

Safety Endpoint

Safety endpoints were defined as the presence of any short-term adverse event(s), such as any death and any adverse event(s) within 30 days of donation, and long-term adverse events, such as any secondary malignancy, autoimmune and cardiovascular disease, and any other pathology occurring at any time postdonation related to HSC collection. All donors were asked to rate G-CSF–related adverse events as mild (grade 1), moderate (grade 2), or severe (grade 3). Discontinuation of a G-CSF–related adverse event was defined as grade 4. The severity of adverse events was recorded according to the Common Terminology Criteria of Adverse Events, version 4.

HDs were monitored daily by clinical examination and laboratory analyses during G-CSF administration and every 3 to 4 days during follow-up until the normalization of blood counts. Subsequently, subjects were monitored prospectively by clinical examination and hematological parameters every 6 months during the first year of follow-up and once a year for at least 10 years. If donors were unable to come to the hospital, they were solicited yearly by mail and/or by telephone to send the most recent hematological analyses. All data were collected in a dedicated Excel database. The final grade of adverse effects was provided by the clinician.

Efficacy and safety endpoints were evaluated in the entire population and according to age group. HDs were grouped according to age as HDs-1, patients <50 years; HDs-2, patients aged 50 to 59 years; and HDs-3, patients aged ≥60.

Statistical Analysis

Data were reported for the whole patient population and according to HD age group. HDs groups (HDs-1, HDs-2, and HDs-3) were summarized by appropriate statistics consisting of median, minimum, and maximum for continuous variables, whereas categorical variables were reported in tables as absolute and relative frequencies and in graphs as relative frequencies. One-way analysis of variance was used for the analysis of continuous variables. Pearson's chi-square test or Fisher's exact test, if deemed more appropriate, was used for the analysis of categorical outcomes. For recipient patients, age, type of tumor, and gender were recorded.