Biol Blood Marrow Transplant ■■ (2018) ■■–■■

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

Higher Donor Apheresis Blood Volumes Are Associated with Reduced Relapse Risk and Improved Survival in Reduced-Intensity Allogeneic Transplantations with Unrelated Donors

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Article history:
Received 22 August 2017
Accepted 28 January 2018

Key Words:
Apheresis
Allogeneic
Transplantation
Unrelated donor
Reduced-intensity
conditioning

A B S T R A C T

Allogeneic hematopoietic stem cell transplantation (HSCT) with reduced-intensity conditioning (RIC) offers a curative option for patients with hematologic malignancies who are unable to undergo myeloablative conditioning, but its success is limited by high rates of relapse. Several studies have suggested a role for T cell doses in peripheral blood stem cell grafts in RIC HSCT. Because T cell dose is typically not known until after the collection, and apheresis blood volume is easily modifiable, we hypothesized that higher donor apheresis blood volumes would improve transplantation outcomes through an effect on graft composition. Thus, we analyzed the relationships between apheresis volume, graft composition, and transplantation outcomes in 142 consecutive patients undergoing unrelated donor allogeneic RIC HSCT. We found that apheresis volume ≥15 L was associated with a significantly decreased risk of relapse (adjusted hazard ratio [aHR], .48; 95% confidence interval [CI], .28 to .84]; $P = .01$) and improved relapse-free survival (aHR, .56; 95% CI, .35 to .89; $P = .02$) and overall survival (aHR, .55; 95% CI, .34 to .91; $P = .02$). A high apheresis volume was not associated with increased rates of acute or chronic graft-versus-host disease. These results demonstrate that an apheresis volume of at least 15 L is independently predictive of improved transplantation outcomes after RIC allogeneic HSCT.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) with reduced-intensity conditioning (RIC) offers a curative option for patients with hematologic malignancies who are ineligible for myeloablative HSCT. However, 25% to 60% of patients who undergo RIC HSCT experience disease recurrence [1-9]. Reducing the risk of relapse is critical to improving overall survival (OS) for patients with hematologic malignancies treated with RIC allo-HSCT.

RIC allo-HSCTs generally use peripheral blood stem cell (PBSC) grafts, collected by apheresis. Several recent studies have found that the graft composition, other than $CD34^+$ cells, is predictive of transplantation outcomes after RIC. Our group demonstrated that a high $CD8^+$ T cell dose is significantly correlated with a lower risk of relapse and improved OS, without increasing the risk for graft-versus-host disease (GVHD) in 200 patients conditioned with fludarabine and busulfan i.v. (Flu/Bu2) [10]. A similar association between $CD8^+$ T cell dose and reduced risk of relapse was demonstrated in a smaller study of nonmyeloablative conditioning [11]. A study by the National Marrow Donor Program that included both myeloablative and RIC transplantations demonstrated a relationship between $CD8^+$ T cell dose and superior platelet recovery, again without increased risk for GVHD [12]. In addition, several studies have found a significant association between the total nucleated cell (TNC) dose and OS after RIC transplants, independent of the $CD34^+$ cell dose [13,14]. These studies led us to question whether in the RIC setting, the CD34 dose is the most appropriate parameter for defining an optimal graft. It seems that the abundance of other cell types is a modifiable factor that might impact transplantation outcomes.

This consideration is particularly important in unrelated donor transplantations, for which grafts are collected at many

Financial disclosure: See Acknowledgments on page 5.
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https://doi.org/10.1016/j.bbmt.2018.01.037
1083-8791/

donor centers with varying practices. Collection centers do not share a uniform practice for measuring graft content, and tests for graft composition may vary significantly between laboratories, introducing inconsistency into reported cell doses. Furthermore, cell dose information is typically not available until after collection is complete. However, it has been observed that the TNC and T cell doses are directly correlated with the donor apheresis blood volume processed during stem cell collection [10,15-18]. Thus, standardizing collection practices by defining an optimal range of apheresis blood volume can be a simplified and consistent method to which collection centers could universally conform.

We hypothesized that a higher apheresis volume would be associated with decreased relapse risk and improved survival, potentially through higher T cell doses. Here we examined whether higher apheresis blood volumes were correlated with graft T cell content in unrelated donor transplants, and whether this led to improvement in OS and a decrease in relapse rate. To examine this, we retrospectively analyzed a single-center cohort of consecutive patients who received an allogeneic transplant from an unrelated donor with a uniform RIC regimen.

METHODS

Patients and Treatment

We collected data on 146 consecutive adult patients who underwent a first allo-HSCT with RIC and PBSC grafts from unrelated donors at the Hospital of the University of Pennsylvania between August 2006 and February 2015. Four patients were excluded from the analysis owing to incomplete donor apheresis data. The Institutional Review Board of the University of Pennsylvania approved the study. Patients provided informed consent for data collection before transplantation.

All patients received uniform conditioning with fludarabine 120 mg/m^2 i.v. and busulfan 6.4 mg/kg i.v. (Flu/Bu2) and standard GVHD prophylaxis, which was either tacrolimus- or cyclosporine-based. Patients did not receive T cell-depleting agents or prophylactic donor lymphocyte infusions, and all patients received standard antimicrobial prophylaxis.

All donors had PBSC grafts collected after G-CSF mobilization at donor centers outside of the University of Pennsylvania. We requested a minimum of 4×10^6 CD34$^+$ cells/kg based on the recipient's weight. Actual donor apheresis volumes for domestic donors were provided by the National Marrow Donor Program. The volumes for international donors were provided by individual international registries. Cell doses in the infused products were measured by flow cytometry at the University of Pennsylvania using standard procedures.

Clinical Outcomes

We measured time to disease relapse, grade II-IV acute GVHD, moderate to severe chronic GVHD, nonrelapse mortality, relapse-free survival (RFS), and OS. The Disease Risk Index (DRI) was calculated for each patient using published criteria [19]. Data collection for all outcomes was censored at last patient contact or second transplant, and at time of donor lymphocyte infusion for GVHD outcomes. Disease relapse was defined as morphologic, cytogenetic, or radiologic evidence of disease demonstrating pretransplantation characteristics. Disease status evaluations, including bone marrow biopsies and appropriate imaging studies, were routinely performed at day +100, or earlier in patients with signs indicating early relapse. The Consensus Conference criteria and National Institutes of Health criteria were used for acute and chronic GVHD grading, respectively [20,21].

Statistical Analysis

The Pearson and Student *t* test were used to assess correlations between donor apheresis volume and clinical variables. A classification and regression tree (CART) analysis was used to identify the optimal cutoff for apheresis blood volume that separates the survival function. Predictors of time to relapse, nonrelapse mortality, and GVHD were identified using competing-risks regression analyses, allowing for death without the event as a competing risk. Predictors of time-to-event outcomes were identified using Cox regression or competing-risks regression where appropriate. Significant independent predictors were identified using multivariable models. Variables that exhibited univariate significance of $P < .20$ were considered for multivariable analysis using backward elimination to minimize the number of variables in each model. Multivariable regression models were compared using the likelihood ratio test. Analyses were conducted using Stata version 13.1 (StataCorp, College Station, TX).

RESULTS

Patients, Donors, and Stem Cell Collections

Patient, disease, and transplantation characteristics for 142 evaluable patients are presented in Table 1. The median duration of follow-up was 35.7 months. Diseases included acute myelogenous leukemia (n = 65), myelodysplastic syndrome (n = 33), lymphoma (n = 21), and others (n = 23), and the median recipient age was 64 years (range, 21 to 74 years). The median donor age was 29 years (range, 18 to 58 years); 80% of the donors were HLA-matched, and the other 20% had a single-allele mismatch. Patients were collected at domestic (62%) or international (38%) donor centers over 1 day (87%) or 2 days (13%) of apheresis.

There was significant variability in apheresis blood volumes (Figure 1). Median apheresis blood volume was 18.1 L (range,

Table 1
Patient Characteristics

Variable	Value
Recipient age, yr, median (range)	64 (21-74)
Donor age, yr, median (range)	29 (18-58)
Donor collection center location, n (%)	
Domestic	88 (62)
International	54 (38)
Apheresis blood volume, L median (range)	18.1 (7.7-30)
Apheresis volume by donor center location, median (range)	
Domestic centers	20 (10-30)
International centers	15 (7.7-27.2)
Days of collection, n (%)	
1 day	123 (87)
2 days	19 (13)
Male recipients, n (%)	81 (57)
Males donors, n (%)	87 (61)
Diagnosis, n (%)	
AML	65 (46)
MDS	33 (23)
NHL	16 (11)
ALL	9 (6)
CLL	5 (4)
HL	5 (4)
MF	4 (3)
CML	2 (1)
PLL	2 (1)
MM	1 (1)
HLA compatibility, n (%)	
10/10 match	113 (80)
Single-allele mismatch	29 (20)
ABO compatibility, n (%)	
Match	71 (50)
Mismatch	70 (49)
Unknown	1 (1)
GVHD prophylaxis, n (%)	
Tacrolimus-based	127 (89)
Cyclosporine-based	15 (11)
Era, n (%)	
2006-2010	73 (51)
2011-2015	69 (49)
TNC dose, cells/kg $\times 10^8$, median (range)	9.7 (1.3-22.4)
CD34$^+$ cell dose, cells/kg $\times 10^6$, median (range)	7.0 (1.8-21.4)
CD3$^+$ cell dose, cells/kg $\times 10^8$, median (range)	2.7 (.4-8.1)
CD4$^+$ cell dose, cells/kg $\times 10^8$, median (range)	1.5 (.2-5.4)
CD8$^+$ cell dose, cells/kg $\times 10^8$, median (range)	.7 (.06-2.2)

HLA was matched using high-resolution typing for HLA-A, -B, -C, -DRB1, and -DQB1.
ALL indicates acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; HL, Hodgkin lymphoma; MDS, myelodysplastic syndrome; MF, myelofibrosis; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; PLL, prolymphocytic leukemia.