Biol Blood Marrow Transplant 21 (2015) 646–652

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

A Two-Step Approach to Myeloablative Haploidentical Transplantation: Low Nonrelapse Mortality and High Survival Confirmed in Patients with Earlier Stage Disease

Dolores Grosso [1,*], Sameh Gaballa [1,†], Onder Alpdogan [1], Matthew Carabasi [1], Joanne Filicko-O'Hara [1], Margaret Kasner [1], Ubaldo Martinez-Outschoorn [1], John L. Wagner [1], William O'Hara [2], Shannon Rudolph [1], Inna Chervoneva [3], Beth Colombe [4], Patricia Cornett Farley [5], Phyllis Flomenberg [6], Barbara Pro [1], Manish Sharma [1], Wenyin Shi [7], Mark Weiss [1], Neal Flomenberg [1]

[1] *Department of Medical Oncology, Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, Pennsylvania*
[2] *Department of Pharmacy, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania*
[3] *Department of Pharmacology and Experimental Therapeutics, Thomas Jefferson University, Philadelphia, Pennsylvania*
[4] *Tissue Typing Laboratory, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania*
[5] *Clinical Laboratory for Cellular Therapy, Thomas Jefferson Hospital, Philadelphia, Pennsylvania*
[6] *Department of Infectious Diseases, Thomas Jefferson University, Philadelphia, Pennsylvania*
[7] *Department of Radiation Oncology, Thomas Jefferson University, Philadelphia, Pennsylvania*

Article history:
Received 20 October 2014
Accepted 17 December 2014

Key Words:
Haploidentical stem cell transplantation
T cell dosing
Donor availability
Disease-free survival
Nonrelapse mortality

A B S T R A C T

Haploidentical hematopoietic stem cell transplantation (HSCT) is an attractive alternative donor option based on the rapid availability of an acceptable donor for most patients and decreased cost compared with costs of other alternative donor strategies. The safety of haploidentical HSCT has increased in recent years, making it ethically feasible to offer to patients with earlier stage disease. We developed a 2-step approach to haploidentical HSCT that separates the lymphoid and myeloid portions of the graft, allowing fixed T cell dosing to improve consistency in outcome comparisons. In the initial 2-step trial, the subset of patients without morphologic disease at HSCT had high rates of disease-free survival. To confirm these results, 28 additional patients without evidence of their disease were treated and are now 15 to 45 (median, 31) months past HSCT. To date, the 2-year cumulative incidence of nonrelapse mortality is 3.6%, with only 1 patient dying of nonrelapse causes, confirming the safety of this approach. Based on low regimen toxicity, the probabilities of disease-free and overall survival at 2 years are 74% and 77%, respectively, consistent with the findings in the initial trial and supporting the use of this approach in earlier stage patients lacking a matched related donor.

INTRODUCTION

The availability of a suitable matched related donor for patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT) has decreased in the last decade because of downward trends in nuclear family size [1,2] and an increase in the number of mixed parentage families, especially in younger segments of the population [3]. Conversely, older patients are increasingly undergoing HSCT but have limited matched related donor options [4] because of advanced sibling age and comorbidities. Based on these trends, there is a crucial need to safely treat patients requiring HSCT using alternative donors.

Haploidentical HSCT is an attractive alternative donor option for many reasons. Unlike HSCT using unrelated adult donors or cord blood, there are no additional search, storage, or transportation fees. The local selection and use of a haploidentical donor avoids delays in treatment and there is greater control of cell doses. Most patients will have a suitable haploidentical family donor, extending HSCT therapy to almost every segment of the population, including minority or mixed-ancestry patients, many of whom are unlikely to

Financial disclosure: See Acknowledgments on page 651.
* Correspondence and reprint requests: Dolores Grosso, DNP, Jefferson Medical Oncology, 834 Chestnut Street, Suite 320, Philadelphia, PA 19107.
E-mail address: dolores.grosso@jefferson.edu (D. Grosso).
† Current address: Sameh Gaballa, Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX.

http://dx.doi.org/10.1016/j.bbmt.2014.12.019
1083-8791/

have a fully matched adult donor in unrelated donor registries [5,6]. The expanded pool of prospective haploidentical donors for each patient allows optimization of donor selection based on factors other than human leukocyte antigen (HLA) matching, such as cytomegalovirus (CMV) serostatus, gender differences, or killer immunoglobulin-like (KIR) ligand mismatching [7].

Historically, outcomes after haploidentical HSCT have been negatively affected by delayed post-HSCT immune recovery, a result of the necessity to attenuate T cells in the mismatched graft to avoid life-threatening graft-versus-host disease (GVHD) [8-10]. Recent advances in T cell–containing haploidentical approaches have improved immune reconstitution and outcomes [11]. However, the heterogeneity of HSCT approaches, especially the variable dosing of T cells, precludes the ability to compare outcomes among haploidentical approaches and between haploidentical HSCT versus HSCT using other donor sources.

Based on the goals of establishing a safe platform in haploidentical HSCT and examining the impact of T cell dosing on haploidentical HSCT outcomes, we developed a myeloablative 2-step approach in which the lymphoid and myeloid portions of the graft are administered separately to control T cell dosing. In this approach, an unmanipulated donor lymphocyte product (DLI), containing a fixed dose of 2×10^8/kg T cells, is administered after a conditioning regimen of 12 Gy total body irradiation. This quantity of T cells was associated with high engraftment rates and a low incidence of grades III and IV GVHD in the phase I portion of the initial 2-step trial. Within approximately 24 hours of the T cell infusion, an alloreaction consisting of high fever and, in some cases rash and diarrhea, occurs. Two days later, cyclophosphamide (CY) is administered to establish bidirectional tolerance, based on the work of Mayumi et al. [12] and investigators at Johns Hopkins [13,14]. The symptoms associated with the alloreaction universally resolve after CY treatment. The myeloid portion of the graft is given 24 hours after the completion of CY. This 2-step regimen (Figure 1) allows the administration of a fixed dose of T cells, enhancing the reproducibility of outcomes, and avoids the polarizing effects of granulocyte colony–stimulating factor (G-CSF) on donor T cells as growth factors are initiated after the DLI collection. In addition, count recovery is more prompt compared with in post-HSCT CY approaches, as the myeloid portion of the graft is not exposed to CY [15].

In the initial phase I/II haploidentical 2-step trial, a tolerized T cell dose of 2×10^8/kg was associated with low rates of grades III and IV GVHD, consistent engraftment in patients without donor-specific antibodies, and robust immune reconstitution. Based on this low toxicity, the 12 patients without disease at the time of HSCT had a probability of overall survival (OS) of 75% at 3 years at the time of the initial report [16].

The results of this first trial suggested that the 2-step approach to haploidentical HSCT was an appropriate primary alternate strategy for patients with earlier stage disease who were without matched related donors. Although the 2-step platform allows for the exploration of T cell dosing and timing, potentially important strategies to increase disease-free survival (DFS) rates in patients with resistant disease, the goal of this particular second generation 2-step trial was to confirm the safety and efficacy of this method in a larger population of patients without evidence of their malignancy at HSCT.

METHODS

Recipient Consent, Eligibility, Donor Selection

Informed consent was obtained for all of the patients in accordance with the Declaration of Helsinki. The study was approved by the institutional review board of Thomas Jefferson University. Patients had to be in morphologic complete remission to be entered on trial; patients with active disease were not eligible. Other major entry criteria included the availability of a haploidentical related donor that was mismatched for ≥ 2 HLA antigens (HLA-A, -B, -C, -DRB1) in the graft-versus-host direction, adequate organ function as defined by a creatinine clearance of > 60 mL/minute, pulmonary diffusion capacity $\geq$ 50% (corrected for hemoglobin), cardiac ejection fraction $\geq$ 50%, Karnofsky performance status (KPS) $\geq$ 80%, and a hematopoietic cell transplant comorbidity index (HSCT-CI) [17] score of ≤ 5. Patients were excluded if they were pregnant or had evidence of any type of other malignancy. Donors were selected to try to maximize antihost alloreactivity, which was based on factors such as a higher degree of HLA mismatch with the recipient, the presence of recipient/donor KIR ligand mismatches as defined by the Perugia group [18], the presence of a desirable activating KIR haplotype in the donor where applicable [19], and gender mismatches. No patient on trial had a donor-specific HLA antibody.

Collection of Cells, Graft Characteristics, and Processing

Donors underwent apheresis for DLI collection on days -7 and -6. A portion of the unmanipulated DLI product, which contained a fixed dose of 2×10^8 kg of $CD3^+$ cells, was infused after the last fraction of total body irradiation on day -6. After completion of the DLI apheresis, donors received subcutaneous injections of G-CSF, 5 μg/kg twice per day on days −5 through −1, and underwent additional aphereses for hematopoietic stem cells (HSC) on days −2 and −1. The HSC product underwent CD34 selection using the CliniMACS CD34 Reagent System (Miltenyi Biotec, Inc., Auburn, CA). This device was used under Investigational Device Exemption #14336. The targeted cell doses in the HSC product were 2 to 10×10^6/kg $CD\ 34^+$/kg cells and $\leq 5 \times 10^4$/kg $CD3^+$/kg cells. Processing and infusion of the HSC product occurred on day 0.

Definitions

White cell engraftment was defined as an absolute neutrophil count of $\geq .5 \times 10^9$/L for at least 3 consecutive days after transplantation. *Platelet engraftment* was defined as a platelet count of ≥20,000/μL without transfusion for the 7 preceding days. Toxicities were graded using National Cancer Institute Common Toxicity Criteria, Version 3.0. Acute GVHD was scored based on the Glucksberg system [20]. Chronic GVHD was based on the National Institutes of Health Consensus Criteria [21].

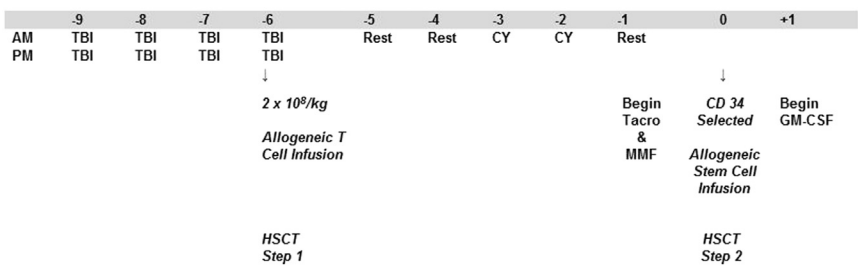

Figure 1. The 2-step regimen. Total body irradiation dose is 1.5 Gy per fraction, for a total dose of 12 Gy; CY dose is 60 mg/kg/day. Tacrolimus (Tacro) and mycophenolate mofetil (MMF) are initiated on day −1 for GVHD prophylaxis.