Biol Blood Marrow Transplant 22 (2016) 895–901

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

Clinical Research: Alternative Donors

Alternative-Donor Hematopoietic Stem Cell Transplantation with Post-Transplantation Cyclophosphamide for Nonmalignant Disorders

Orly R. Klein*, Allen R. Chen, Christopher Gamper, David Loeb, Elias Zambidis, Nicolas Llosa, Jeffrey Huo, Amy E. Dezern, Diana Steppan, Nancy Robey, Mary Jo Holuba, Kenneth R. Cooke, Heather J. Symons

Pediatric Blood and Marrow Transplantation Program, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins Hospital, Baltimore, Maryland

Article history:
Received 31 December 2015
Accepted 1 February 2016

Key Words:
Reduced-intensity conditioning
HLA-haploidentical
Cyclophosphamide
Immunodeficiency
Bone marrow failure syndromes

A B S T R A C T

Allogeneic hematopoietic stem cell transplantation (HSCT) is curative for many nonmalignant pediatric disorders, including hemoglobinopathies, bone marrow failure syndromes, and immunodeficiencies. There is great success using HLA-matched related donors for these patients; however, the use of alternative donors has been associated with increased graft failure, graft-versus-host disease (GVHD), and transplant-related mortality (TRM). HSCT using alternative donors with post-transplantation cyclophosphamide (PT/Cy) for GVHD prophylaxis has been performed for hematologic malignancies with engraftment, GVHD, and TRM comparable with that seen with HLA-matched related donors. There are limited reports of HSCT in nonmalignant pediatric disorders other than hemoglobinopathies using alternative donors and PT/Cy. We transplanted 11 pediatric patients with life-threatening nonmalignant conditions using reduced-intensity conditioning, alternative donors, and PT/Cy alone or in combination with tacrolimus and mycophenolate mofetil. We observed limited GVHD, no TRM, and successful engraftment sufficient to eliminate manifestations of disease in all patients. Allogeneic HSCT using alternative donors and PT/Cy shows promise for curing nonmalignant disorders; development of prospective clinical trials to confirm these observations is warranted.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is curative for many nonmalignant disorders, including hemoglobinopathies, bone marrow failure syndromes, and primary immunodeficiencies (PIDs). Advances in supportive care have greatly improved the success of allo-HSCT for this patient population [1,2]. However, the use of HSCT is limited by the lack HLA-matched donors; only 50% of children in need of an allo-HSCT have an HLA-matched donor, and this number is less than 20% in some minority populations [3]. For patients with certain nonmalignant disorders, an HLA-matched family member may also be affected, further limiting related donor options. Use of alternative donor sources has historically led to increased risk of acute and chronic graft-versus-host disease (GVHD) and graft rejection. Moreover, transplant-related mortality (TRM) remains high, particularly when conventional myeloablative conditioning is used [4]. Many children with nonmalignant disorders have significant comorbidities at the time of HSCT, including infection and active inflammation, which also contribute to poor outcomes. Reduced-intensity conditioning (RIC) strategies have demonstrated improved survival with decreased TRM [5-7]. Accordingly, allo-HSCT for nonmalignant disorders holds promise as a curative therapy if delivered using a platform that minimizes both short-term and long-term toxicities, maximizes engraftment and cure, and expands the donor pool.

In this context post-transplantation cyclophosphamide (PT/Cy), when administered within a specific time frame after HSCT, selectively depletes the alloreactive donor T cells responsible for GVHD and graft rejection while preserving non-alloreactive resting memory T cells responsible for adaptive immunity and blood stem cells necessary for

Financial disclosure: See Acknowledgments on page 900.

* Correspondence and reprint requests: Orly R. Klein, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins and The Johns Hopkins University School of Medicine, Bunting-Blaustein Cancer Research Building I (CRB 1), 1650 Orleans St., Room 284, Baltimore, MD 21287.
E-mail address: oklein2@jhmi.edu (O.R. Klein).

http://dx.doi.org/10.1016/j.bbmt.2016.02.001
1083-8791/

successful engraftment [8,9]. Use of PT/Cy as GVHD prophylaxis, with or without additional immunosuppression, has been used with alternative donor sources in hematologic malignancies, leading to successful engraftment and rates of GVHD, TRM, and graft failure comparable with HLA-matched related donors [10-12], without increased risk of post-transplant lymphoproliferative disorder [13]. Importantly, HSCT using alternative donors and PT/Cy has been performed for hemoglobinopathies, with GVHD and TRM comparable with that seen with HLA-matched related donors [14,15]. However, reports using this strategy for other nonmalignant pediatric disorders, such as immunodeficiencies and bone marrow failure syndromes, are limited [16,17]. Herein, we describe our institutional experience treating 11 pediatric patients with life-threatening, nonmalignant conditions using alternative donor sources, RIC, and PT/Cy for GVHD prophylaxis.

METHODS

Patients

This study was approved by the institutional review board of The Johns Hopkins Hospital. All pediatric patients (ages 1 month to 21 years) who underwent allo-HSCT at The Johns Hopkins Hospital Bloomberg Children's Center from January 1, 2009 until December 31, 2014 for a nonmalignant condition and for whom there was no available matched sibling donor were included. Nonmalignant conditions included PIDs, hemophagocytic lymphohistiocytosis (HLH), bone marrow failure syndromes, and disorders of erythrocytes or platelets. Alternative donors included matched unrelated donors, mismatched unrelated donors, or haploidentical related donors. Data from medical records, including patient demographics, transplant and clinical data, complications, laboratory and radiologic diagnostic studies, therapy received, overall outcomes, and transplant-related complications, were abstracted and reviewed.

Preparative Regimens

Preparative regimens used are shown in Figure 1. Patients received RIC with alemtuzumab, fludarabine, and melphalan, with or without the addition of low-dose total body irradiation (TBI) of 200 cGy (Figure 1A,B). The exceptions to this conditioning regimen were patients with dyskeratosis congenita (DKC) because of their underlying sensitivity to alkylator chemotherapy, who instead received alemtuzumab, fludarabine, and low-dose TBI (Figure 1C). Alemtuzumab dosing was based on weight, with children >10 kg receiving a total of 48 mg over 3 days, with a test dose of 3 mg followed by a dose escalation schedule of 10 mg/15 mg/20 mg. Patients <10 kg received a total of 33 mg of alemtuzumab over 3 days, with a test dose of 3 mg followed by a dosing schedule of 10 mg/10 mg/10 mg. Patients transplanted before 2013 received alemtuzumab beginning on day −21. From 2013 on, alemtuzumab was given beginning on day −14, at the same doses, based on improved chimerism data with intermediate dosing of alemtuzumab [18]. All patients received fludarabine 150 mg/m^2 divided over 5 days (or 1 mg/kg/day for 5 days for patients <10 kg), either starting on day −8 or day −6. The dosing for melphalan was 140 mg/m^2 (or 3.4 mg/kg for patients <10 kg), either given as a single dose on day −2 or divided over 2 days on days −3 and −2. Low-dose TBI of 200 cGy was given on day −1.

There were 2 exceptions to the above preparative regimens. A patient with immune dysregulation polyendocrinopathy X-linked syndrome received alemtuzumab starting on day −21, followed by fludarabine, melphalan, and low-dose TBI dosed as described above, along with Cy 14.5 mg/kg/day on days −6 and −5. One of the patients with chronic granulomatous disease (CGD) received alemtuzumab starting on day −21,

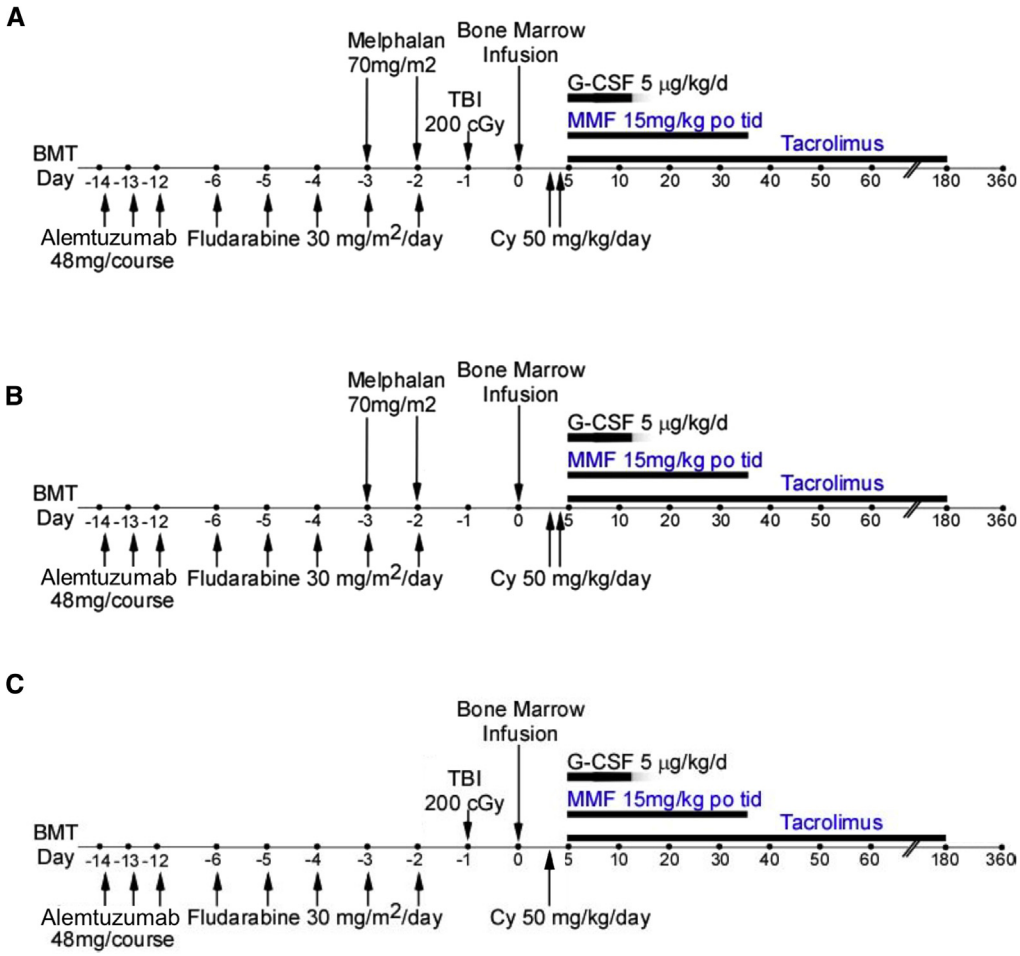

Figure 1. Preparatory regimens, including (A) alemtuzumab, fludarabine, melphalan, TBI; (B) alemtuzumab, fludarabine, and melphalan; and (C) alemtuzumab, fludarabine, and TBI. G-CSF indicates granulocyte colony-stimulating factor; BMT, bone marrow transplantation.