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Outcomes of Donor Lymphocyte Infusion for Treatment of Mixed Donor Chimerism after a Reduced-Intensity Preparative Regimen for Pediatric Patients with Nonmalignant Diseases

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A B S T R A C T

Mixed donor chimerism is increasingly common in the pediatric hematopoietic stem cell transplantation (HSCT) setting because of the increased use of reduced-intensity preparative regimens for nonmalignant diseases. Donor lymphocyte infusion (DLI) is potentially useful in the treatment of mixed donor chimerism, but little are data available on the use of DLI in this setting. We conducted a retrospective review of 27 pediatric patients who received DLI for mixed donor chimerism between January 2006 and December 2010 after receiving a preparative regimen of alemtuzumab, fludarabine, and melphalan. Twenty-one patients (78%) were alive at a median of 35 months post-transplant. Seven patients (26%) sustained full donor chimerism after DLI only at a median of 35 months post-HSCT. Nine patients (33%) continued with mixed donor chimerism (median, 38% [range, 18% to 70%]) at a median of 37 months after DLI only. Five patients underwent unconditioned stem cell boosts or second conditioned transplants after no improvement in donor chimerism was seen following DLI. Donor source appeared to contribute to outcomes after DLI; patients with mismatched unrelated donors had earlier first decline in chimerism and timing of first DLI, a higher response rate to DLI, and an increased rate of graft-versus-host disease (GVHD). There was no response to DLI in patients with matched sibling donors. Ten patients, all with improvement in chimerism after DLI, developed acute GVHD after DLI, with 3 having grade III GVHD. Three patients developed chronic GVHD after DLI. These data illustrate the potential efficacy of DLI in the treatment of mixed donor chimerism after a reduced-intensity preparative regimen.

INTRODUCTION

Mixed donor chimerism, the coexistence of donor and recipient hematopoiesis after allogeneic stem cell transplantation, is increasingly seen in the pediatric setting because of the upsurge in use of reduced-intensity conditioning regimens for nonmalignant diseases. Mixed donor chimerism is associated with a decreased risk of graft-versus-host disease [1-5], but patients with mixed donor chimerism are at increased risk for graft loss and recurrence of the original disease [4]. Factors contributing to the development of mixed donor chimerism include the patient's underlying diagnosis, the composition and dose of the cell graft, and the intensity of the preparative regimen and use of serotherapies that deplete graft lymphocytes [6,7].

Although full donor chimerism is necessary to cure most malignant conditions, it is now apparent that partial donor chimerism is sufficient to eradicate the manifestations of many nonmalignant diseases, particularly immunodeficiencies and hemoglobinopathies [6,8,9]. With hemophagocytic lymphohistiocytosis, a patient may display no evidence of the original disease with a donor chimerism as low as 20% [6]. The decreased mortality and late effects of reduced-intensity preparative regimens are especially attractive in the treatment of diagnoses in which the patient population is predominantly pediatric and full donor chimerism is not required. Specifically, Marsh et al. [6] and Cooper et al. [8] reported improved outcomes when using a reduced-intensity preparative regimen for hemophagocytic lymphohistiocytosis. However, the decreased toxicity of reduced-intensity preparative regimens is traded for an increased risk of nonengraftment, mixed donor chimerism, and graft loss.

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Table 1
Transplant Characteristics of Patients Undergoing DLI for Mixed Donor Chimerism

Characteristic	All Patients
Diagnosis	
Hemophagocytic lymphohistiocytosis	16
Severe combined immunodeficiency	3
Omenn's syndrome	1
X-linked lymphoproliferative disease	3
Common variable immunodeficiency	1
Hurler's syndrome	1
Langerhans cell histiocytosis	1
IPEX	1
Sex	
Male	20
Female	7
Donor source	
Matched sibling bone marrow	4
8/8 unrelated donor	14
7/8 unrelated donor	8
6/8 unrelated donor	1
Median age at transplant, yr (range)	1.2 (.31-17)
Preparative regimen	
Proximal alemtuzumab	21
Distal alemtuzumab	6

IPEX indicates Immune Dysregulation, polyendocrinopathy, enteropathy, X-linked.

Mixed donor chimerism is often treated with immune modulation via taper of immunosuppression and donor lymphocyte infusion (DLI) because of the concern for graft loss [10-13]; however, both treatments increase the risk for graft-versus-host disease (GVHD). Currently, very little data are found in the literature on outcomes after DLI for mixed donor chimerism to help guide the physician in managing this complication. In this retrospective study we investigated the characteristics and outcome of patients who received DLI for nonmalignant disease after a reduced-intensity preparative regimen of alemtuzumab, fludarabine, and melphalan. To our knowledge, this is the first study in a relatively large pediatric cohort detailing the use and outcomes of DLI for management of mixed donor chimerism after reduced-intensity preparative regimens composed of predominantly pediatric patients with nonmalignant diseases.

METHODS

A retrospective review was conducted on all patients who received DLIs between January 2006 and December 2010. Patients were included in this series if they received DLIs for mixed donor chimerism after a preparative regimen of alemtuzumab, fludarabine, and melphalan.

Patients and Transplant Characteristics

Timing and dose of alemtuzumab was based on physician preference. Most patients received proximal alemtuzumab, with dosing starting anywhere from day −12 to day −7. Six patients received distal alemtuzumab with dosing starting before day −20. Most patients received fludarabine 150 mg/m^2 and melphalan 140 mg/m^2. All patients received bone marrow grafts. In 25 patients, GVHD prophylaxis consisted of cyclosporine or tacrolimus and methylprednisolone 1 to 2 mg/kg/day with planned methylprednisolone taper starting day 28 in the absence of mixed chimerism or GVHD. One patient received GVHD prophylaxis with mycophenolate and prednisone, and 1 received cyclosporine, methylprednisolone and methotrexate with methotrexate dosed on days +1, +3, and +6. Table 1 shows patient and transplant characteristics.

Donor Chimerism Measurement

Whole blood total donor chimerism was monitored frequently (most commonly weekly) from the time of engraftment. In patients with opposite sex donors, chimerism was monitored by fluorescent in situ hybridization with X and Y chromosome probes. In patients with same-sex donors, donor chimerism was monitored with PCR amplification of 15 highly variable short tandem repeats followed by capillary electrophoresis for size discrimination to determine the various alleles at 15 individual loci as well as chromosome X and Y specific products. Chimerism sorted by cell subsets was not routinely obtained but was performed when clinically indicated at the discretion of the attending physician. All whole blood chimerism studies were performed in the clinical genetics laboratory at Cincinnati Children's Hospital.

Donor Lymphocyte Infusion

Decisions to give DLIs, dose of DLIs, and timing of DLIs, were not prescribed and were at the discretion of the attending physician. Lymphocytes for DLI were either frozen aliquots collected from the donor at the time of the original harvest or were collected peripherally from the donor before DLI.

Definitions and Outcomes

Complete response to DLI was defined as a donor chimerism of 98% to 100%. Response to DLI was defined as a donor chimerism increase of at least 20% after DLI. Loss of donor chimerism was defined as a decrease of at least 10% from peak donor chimerism after hematopoietic stem cell transplantation (HSCT). Descriptive statistics were used to look for outliers and assess distributional properties.

The Mann-Whitney U test and exact Kruskal-Wallis test were used to examine the differences between groups. Variables examined were days post-transplant for first decreased engraftment, days post-transplant for first DLI, last engraftment before first DLI, age at first DLI, and number of DLIs. Results are presented as medians with ranges and P values where appropriate. Logistic regression was used to test if intervention timing was a significant predictor of complete response versus no complete response. Because of the small patient numbers and descriptive nature of the study, no adjustments were made for multiple testing.

Analyses were performed using SAS statistical software package, version 9.3 (SAS Institute, Inc., Cary, NC). Significance was set a priori at $\alpha = .05$. Acute and chronic GVHD were assessed and classified by standardized published criteria [14,15].

RESULTS

Patients

One hundred twenty-six patients underwent transplant for nonmalignant disease with a preparative regimen of alemtuzumab, fludarabine, and melphalan from 2006 to 2010. Of these 126 patients, 27 (21.4%) received DLI for mixed donor chimerism after having no improvement in chimerism with immunosuppression taper. The patients who developed mixed donor chimerism but did not receive DLI were not included in this series.

Institutional Approach to Management of Mixed Donor Chimerism

Because management of waning donor chimerism was not prescribed, there was some heterogeneity in treatment; however, there was broad institutional agreement on the approach to mixed donor chimerism. Initial management of waning donor chimerism was generally a rapid taper (over 1 to 2 weeks) or abrupt discontinuation of corticosteroids, followed by taper of calcineurin inhibitors. In the absence of GVHD, DLI followed within 3 or 4 weeks of discontinuation of immunosuppression if there was not stabilization of donor chimerism. The rate at which physicians moved through these interventions varied, with donor source, level and rate of decline of donor chimerism, underlying disease, and history of GVHD among the variables contributing to the decision. In the absence of GVHD, patients who did not achieve stabilization or improvement in donor chimerism generally received subsequent DLIs with escalating dose of T cells at the discretion of the attending physician.

General Characteristics of DLI Therapy

Twenty-seven patients received a total of 88 DLIs. The first DLI was given at a median of 98 days post-transplant (range, 44 to 230). Other characteristics of DLI are displayed in Table 2. Patients received a median of 2 DLIs (range, 1 to 12) with a median interval between infusions of 21 days