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Clinical Research: Alternative Donors

Durable Chimerism and Long-Term Survival after Unrelated Umbilical Cord Blood Transplantation for Pediatric Hemophagocytic Lymphohistiocytosis: A Single-Center Experience

Sachit A. Patel [1], Heather A. Allewelt [2], Jesse D. Troy [3], Paul L. Martin [4], Timothy A. Driscoll [4], Vinod K. Prasad [4], Joanne Kurtzberg [3,4], Kristin M. Page [4], Suhag H. Parikh [4,*]

[1] *Department of Pediatrics, University of Nebraska Medical Center, Omaha, Nebraska*
[2] *Department of Pediatrics, Florida Hospital, Orlando, Florida*
[3] *Duke Translational Research Institute, Durham, North Carolina*
[4] *Department of Pediatrics, Division of Pediatric Blood and Marrow Transplantation, Duke University Medical Center, Durham, North Carolina*

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A B S T R A C T

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening disorder of immune dysregulation characterized by fever, hepatosplenomegaly, cytopenias, central nervous system disease, increased inflammatory markers, and hemophagocytosis. Currently, allogeneic hematopoietic stem cell transplantation is the only curative approach for patients with HLH, with reported survival ranging from 50% to 70% with myeloablative conditioning (MAC) regimens. However, donor availability and transplantation-related mortality associated with conventional MAC are major barriers to success. Unrelated umbilical cord blood transplantation (UCBT) provides a readily available alternative donor source for patients lacking matched related donors. Accordingly, we report the results of UCBT in 14 children treated between 1998 and 2016. All children received standard HLH chemotherapy before UCBT. The median age at diagnosis was 2.7 months (range, .8 to 10.4) and at transplantation was 7.5 months (range, 3.8 to 17). Ten patients received MAC with busulfan/cyclophosphamide/etoposide /antithymocyte globulin (ATG) (n = 5), busulfan/cyclophosphamide /ATG (n = 4), or busulfan /melphalan/ATG (n = 1). Four patients received reduced-toxicity conditioning (RTC) with alemtuzumab/fludarabine/melphalan/hydroxyurea ± thiotepa. Cord blood units were mismatched at either 1 (n = 9) or 2 (n = 5) loci and delivered a median total nucleated cell dose of 11.9×10^7/kg (range, 4.6 to 27.9) and $CD34^+$ dose of 3.1×10^5/kg (range, 1.1 to 6.8). The cumulative incidence of neutrophil engraftment by day 42 was 78.6% (95% confidence interval [CI], 42.9% to 93.4%) with a median of 19 days (range, 13 to 27), and that for platelet (50,000) engraftment by day 100 was 64.3% (95% CI, 28.2% to 85.7%) with a median of 51 days (range, 31 to 94). Six patients developed either grade II (n = 5) or grade IV (n = 1) acute graft-versus-host disease (GVHD); no extensive chronic GVHD was seen. Ten patients (71.4%) are alive and well at a median of 11.2 years after transplantation (range, .85 to 18.25), 9 of whom maintain sustained full donor chimerism after a single UCBT, whereas 1 patient with autologous recovery after first UCBT with RTC has achieved full donor chimerism after a second UCBT with MAC. This series demonstrates that, in combination with standard HLH therapy, UCBT after MAC or RTC conditioning can provide long-term survival with durable complete donor chimerism comparable to that of conventional donors. UCBT should be considered for patients with HLH lacking a fully matched related or unrelated adult donor.

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare and often fatal syndrome of immune dysregulation and hyperactivation caused by defects in cytotoxicity of natural killer cells and cytotoxic T lymphocytes. Clinical manifestations include fever, hepatosplenomegaly, cytopenias, hemophagocytosis and, in some cases, neurologic manifestations [1-3]. Laboratory abnormalities include elevated ferritin, triglycerides, transaminases, bilirubin, soluble IL 2–receptor alpha-chain, and coagulopathy. Diagnosis is made by clinical presentation and fulfillment of 5 of 8 criteria as outlined in the HLH-2004 treatment protocol [4]. The disease

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* Correspondence and reprint requests: Suhag H. Parikh, MD, Department of Pediatrics, Division of Pediatric Blood and Marrow Transplantation, Duke University Medical Center, Box 3350, Durham, NC 27710.
E-mail address: suhag.parikh@duke.edu (S.H. Parikh).

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can be genetically inherited or acquired after infections, malignancy, or autoimmune processes. Familial disease can be associated with 1 of several genetic defects (including mutations in PRF1, MUNC 13-4, STX11, STXBP2, XIAP, SH2D1A, etc.) with HLH as the sole manifestation. Additionally, HLH can be a part of immunodeficiency syndromes like Griscelli syndrome or Chediak-Higashi syndrome, where HLH is frequently, but not always, seen [5-8].

Although therapy with corticosteroids, etoposide, and cyclosporine is often effective at inducing disease remission and prolonging survival, the only cure for familial or primary HLH is allogeneic hematopoietic stem cell transplantation (HSCT) [4]. The procedure is also recommended in cases of HLH with central nervous system (CNS) involvement and in the setting of recurrent or progressive HLH despite first-line chemoimmunotherapy [9]. Although effective in curing a substantial number of patients, the conventional busulfan-based myeloablative preparative regimens have been associated with a very high rate of transplantation-related mortality (TRM) (~30% to 40%) and high incidence of acute liver and lung toxicities [10-14]. Reduced-intensity conditioning (RIC) using alternatives to busulfan, such as melphalan and treosulfan, have demonstrated superior overall survival [15,16]. However, a higher incidence of graft failure and mixed donor chimerism in these patients has necessitated frequent post-transplantation interventions, such as donor lymphocyte infusions and second transplantations [17,18].

Another challenge for these patients is finding a suitable donor quickly. Several patients lack conventional bone marrow donors, for whom partially mismatched unrelated umbilical cord blood transplantation (UCBT) can be an attractive alternative because of timely availability, need for less stringent HLA matching, and adequate cell dose in this population of young patients. There are limited data regarding long-term outcomes for pediatric HLH patients receiving UCBT [14,19-21]. In this report, we describe the outcomes after UCBT in children with HLH treated at a single center.

METHODS

Patients

Between 1998 and 2016, 14 pediatric patients lacking matched bone marrow donors underwent first single UCBT as definitive treatment for familial HLH at Duke University Medical Center. Data collection and retrospective analysis for this study were approved by the Duke University Medical Center institutional review board. Written assent or informed consent was obtained from all parents/caretakers, in accordance with the Declaration of Helsinki. Preliminary data on patients 11, 12, and 13 have been included in previous publications [22,23].

Donors

Cord blood units were selected based on HLA class I (A, B) intermediate-resolution and HLA class II (DRB1) high-resolution allelic level typing. The minimum requirement for precryopreserved total nucleated cell count was $> 3 \times 10^7$/kg and the cord blood donor had to be ≥ 4/6 HLA match with the recipient. Precryopreservation graft characteristics were obtained from the supplying cord blood banks. The Duke University Hospital stem cell laboratory thawed and performed testing of cord blood units providing the post-thaw data.

Conditioning Regimen

Ten patients received busulfan-based myeloablative conditioning (MAC). Five patients received busulfan 1 mg/kg every 6 hours for 16 doses from days –9 to –6; cyclophosphamide 50 mg/kg/dose from days –5 to –2 with mesna; etoposide 150 mg/m^2/dose from days –5 to –3, and equine antithymocyte globulin (eATG) 30 mg/kg/dose from days –3 to –1. Four patients received busulfan/cyclophosphamide/eATG without etoposide. One patient received busulfan, melphalan (45 mg/m$^2 \times 3$), and eATG as previous described [24]. Busulfan was administered by oral and intravenous route in 7 and 3 patients, respectively. Busulfan pharmacokinetics were studied after the first dose and doses 5 to 16 were adjusted to target steady state concentration of 600 ng/mL to 900 ng/mL. Four patients received reduced-toxicity conditioning (RTC) with alemtuzumab 1 mg/kg/dose i.v. on 3 successive days (–21 to –19), after an initial test dose of .2 mg/kg on day –22: hydroxyurea 30 mg/kg/day orally from day –22 to day –10; fludarabine 30 mg/m^2/day i.v. from days –9 to –5; melphalan 70 mg/m^2/day i.v. on days –4, –3. Three of these patient also received thiotepa 200 mg/m^2 i.v. on day –2. After thawing and washing, the cord blood units were infused intravenously on day 0, as previously described [25,26].

Graft-versus-Host Disease Prophylaxis and Treatment

Graft-versus-host disease (GVHD) prophylaxis for RTC transplantations started on day –3 with i.v. tacrolimus and i.v. mycophenolate 45 mg/kg/day. Tacrolimus levels were maintained between 8 ng/mL and 15 ng/mL. The remaining patients received cyclosporine and methylprednisolone 1 mg/kg/day (n = 9) or cyclosporine and mycophenolate (n = 1). Cyclosporine levels were maintained between 200 ng/mL and 300 ng/mL. For patients without evidence of GVHD, mycophenolate was discontinued on day 45, steroids were tapered after day 30, and calcineurin inhibitors were tapered starting at 9 months after transplantation. Acute and chronic GVHD were scored and graded in accordance with standard criteria [27,28]. Patients with grade 1 acute GVHD were treated with topical therapy while patients with grades 2 to 4 acute GVHD were treated with systemic methylprednisolone with or without additional agents.

Transplantation and Supportive Care

All patients were hospitalized in the pediatric blood and marrow transplant unit of Duke University Medical Center for conditioning and through engraftment and post-transplantation stabilization. All patients had central venous catheter access before transplantation. Levetiracetam or phenytoin was administered as seizure prophylaxis in patients while receiving busulfan. Baths were prescribed after thiotepa every 4 hours for 24 hours. Antiviral prophylaxis included acyclovir; antifungal prophylaxis included amphotericin B before 2003 (6 patients) and voriconazole thereafter (7 patients). Prophylaxis for veno-occlusive disease (VOD) was continuous low-dose heparin infusion (100 units/kg/day) from the day of initiating chemotherapy until day +28 for all patients except unique patient number (UPN) 14, who received ursodiol. Standard pneumocystis jiroveci pneumonia prophylaxis, nutritional, and transfusion support were administered as previously described [25].

All patients received intravenous immunoglobulin (500 mg/kg/dose) weekly until day + 100. Filgrastim (Amgen, Thousand Oaks, CA) was administered at 5 mcg/kg/day to 10 mcg/kg/day from day +1 and weaned after engraftment. Cytomegalovirus DNA was monitored weekly after transplantation. Two patients received irradiated granulocyte colony–stimulating factor–mobilized granulocytes from parental donors until engraftment, because of history of nonhealing deep perirectal ulcers and colostomy wound, respectively, at the time of transplantation.

Post-Transplantation Assessments

Donor cell chimerism was measured at engraftment, day 100, every 3 months during the first post-transplantation year, and yearly thereafter. Chimerism was confirmed by restriction fragment length polymorphism, microsatellite markers, HLA, or XY fluorescent in situ hybridization–based tests. Patients had organ function and immunologic evaluation every 3 months during the first year and annually thereafter. Patients also had serum ferritin and serum soluble IL-2 receptor levels measured wherever possible.

Statistical Analysis

We used primarily descriptive methods to evaluate the post-transplantation experience of this cohort. Continuous variables are described by the median and range, and nominal variables are summarized using frequencies and percentages. Overall survival (OS) was estimated using the Kaplan-Meier method. Follow-up time was calculated from the day of transplantation to the date of death or the date the patient was last known to be alive. Neutrophil and platelet engraftment were described by estimating the cumulative incidence function with death as a competing event. Analyses were performed in SAS 9.4 (SAS Institute, Cary, NC) and R 3.1.2.3.

RESULTS

Patient Characteristics

From 1998 to 2016, 14 patients with familial HLH underwent UCBT. All patients met the diagnostic criteria for HLH in accordance with the HLH-2004 protocol (Table 1) [4]. The median age of our cohort at the time of diagnosis of HLH was 2.7 months (range, .8 to 10.4). None of the patients had a family history of HLH. Mutation results were available for the last 6 patients, 4 of whom had PRF1 gene mutations