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Unrelated Donor Transplantation in Children with Thalassemia using Reduced-Intensity Conditioning: The URTH Trial

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A B S T R A C T

Allogeneic hematopoietic stem cell transplantation (HSCT) can cure transfusion-dependent thalassemia (TDT). In a multicenter trial we investigated the efficacy of reduced-intensity conditioning (RIC) before unrelated donor (URD) HSCT in children with TDT. Thirty-three children, ages 1 to 17 years, received bone marrow (BM) or umbilical cord blood (UCB) allografts. Median time to neutrophil engraftment was 13 days (range, 10 to 25) and 24 days (range, 18 to 49) and platelet engraftment 23 days (range, 12 to 46) and 50 days (range, 31 to 234) after BM and UCB allografts, respectively. With a median follow-up of 58 months (range, 7 to 79), overall and thalassemia-free survival was 82% (95% CI, .64% to .92%) and 79% (95% CI, .6% to .9%), respectively. The cumulative incidence of grades II to IV acute graft-versus-host disease (GVHD) after BM and UCB allografts was 24% and 44%; the 2-year cumulative incidence of chronic extensive GVHD was 29% and 21%, respectively; 71% of BM and 91% of UCB recipients discontinued systemic immunosuppression by 2 years. Six patients who had Pesaro risk class 2 (n = 5) and class 3 (n = 1) died of GVHD (n = 3), viral pneumonitis (n = 2) and pulmonary hemorrhage (n = 1). Outcomes after this RIC compared favorably with URD HSCT outcomes for TDT and supported engraftment in 32 of 33 patients. Efforts to reduce GVHD and infectious complications are being pursued further.

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INTRODUCTION

β-Thalassemia is caused by mutations that reduce or abrogate β-globin synthesis. The accumulation of excess α-globin tetramers precipitate and trigger ineffective erythropoiesis [1]. Patients with homozygous or compound heterozygous hemoglobin subunit beta null mutations develop severe anemia early in life and require lifelong regular RBC transfusions (transfusion-dependent thalassemia [TDT]) and iron chelation therapy to prevent organ toxicity from accumulated iron [2]. This cumbersome and expensive medical therapy and the associated risks of iron overload and organ toxicity have stimulated investigations of allogeneic hematopoietic stem cell transplantation (HSCT) for this condition and, more recently, gene-modified infusions of autologous hematopoietic cells as curative alternatives.

Conventional myeloablative HSCT for TDT with an HLA-matched sibling donor (MSD) has generated excellent results, especially in young patients with a low Pesaro risk score [3,4]. Alternative-donor HSCT can establish donor erythropoiesis in those who lack an MSD. However, thalassemia patients who are older, with iron-related complications, and undergoing unrelated donor (URD) myeloablative HSCT, especially from cord blood, have a higher risk of toxicities, graft rejection, graft-versus-host disease (GVHD), and transplant-related mortality compared with MSD HSCT [5,6]. Reduced-intensity conditioning (RIC) might represent a strategy to decrease chemotherapy-related organ toxicity from HSCT, especially if the risk of graft rejection can be mitigated by the immunosuppressive intensity of the regimen.

We describe the results of a prospective, multicenter, phase II clinical trial of URD HSCT in children with TDT that was conducted in collaboration with the Thalassemia Clinical Research Network and the Pediatric Blood and Marrow Transplant Consortium. The purpose of the trial was to test our hypothesis that an immunosuppressive RIC regimen was sufficient to establish donor hematopoiesis after URD bone marrow (BM) or umbilical cord blood (UCB) transplantation for TDT. The trial was referred to as the URTH (Unrelated Transplant for Thalassemia) trial.

METHODS

Patients

Children with TDT, ages 1 to 16.99 years, who did not have suitable familial donors were eligible. TDT was established by genotype or was defined as requiring ≥8 erythrocyte transfusions per year of age. The first 20 patients were enrolled in NCT 01005576 and the next 13 in an extension NCT 00920972 (stratum 2) after 2012. Patients were enrolled in sequence, first on the former and next on the latter. Transplant methods and care were the same on both studies. Institutional Review Board approval for both studies was obtained at participating sites. All patients and/or legal guardians assented/consented after detailed discussions about the potential benefits, risks, and alternatives to participating in the trial had been conducted.Patient eligibility was not restricted by the Pesaro risk classification. A liver biopsy was required if RBC transfusions were administered for ≥1 year duration and serum ferritin level was ≥1000 ng/mL; patients with bridging fibrosis were excluded. Eligibility criteria also included adequate organ function, defined as left ventricular ejection fraction > 40% or shortening fraction > 26% by echocardiography; normal pulmonary function (normal diffusion capacity of the lung for carbon monoxide corrected for hemoglobin or oxygen saturation > 97% on room air with normal chest radiograph in the very young); serum creatinine ≤ 1.5 times the upper limit of normal for age or glomerular filtration rate > 70 mL/min/1.73 m^2; serum transaminases < 5 times the upper limit of normal; and a Lansky performance score ≥ 70. Patients with uncontrolled infections, previous HSCT, or pregnant/lactating were excluded.

Stem Cell Sources and HLA Typing

Patients were eligible to enroll if they had no HLA-matched family member and had a suitably matched URD BM or UCB product. URD BM was matched at HLA-A, -B, -C, and -DRB1 loci by high-resolution molecular typing. UCB products were matched at 5 or 6 loci (HLA-A, -B, and -DRB1) after intermediate resolution typing at class I and high-resolution typing at the class II loci. In addition, a minimum prethaw total nucleated cell count ≥ 4×10^7/kg recipient weight was required of the UCB product irrespective of RBC depletion. If suitable BM and UCB products were available, the choice of stem cell source was determined by the treating physician.

RIC Regimen

Iron chelation was withdrawn 48 hours before commencing alemtuzumab. All patients received hydroxyurea (30 mg/kg/day p.o.) between days –50 and –22, alemtuzumab (3-mg test dose and then 10, 15, and 20 mg daily i.v.) between days –22 and –18, fludarabine (30 mg/m^2/day i.v.) between days –8 and –4, thiotepa (4 mg/kg × 2 i.v.) on day –4, and melphalan (140 mg/m^2 i.v.) on day –3. Donor hematopoietic stem cells were administered not less than 36 hours after the last dose of chemotherapy.

GVHD Prophylaxis and Classification

For GVHD prophylaxis, URD BM recipients received tacrolimus or cyclosporine between days –3 and +100 followed by a gradual taper to day +180 (in the absence of GVHD), methotrexate (7.5 mg/m^2 i.v. on days +1, +3, and +6), and methylprednisone/prednisone (1 mg/kg/day) between days +7 and +28. URD UCB recipients received tacrolimus or cyclosporine as above with mycophenolate mofetil (15 mg/kg every 8 hours) between days +1 and +45. Acute GVHD was graded from I to IV, and chronic GVHD was classified as limited or extensive according to Seattle criteria [7,8].

Supportive Care and Infection Prophylaxis

Filgrastim (5 μg/kg/day) was administered from day +7 until the absolute neutrophil count was >1500/μL for 3 consecutive days. Herpes simplex prophylaxis with acyclovir, broad-spectrum antifungal, and antibacterial agents were recommended for 6 months. *Pneumocystis jerovecii* prophylaxis was required for 1 year. Cytomegalovirus (CMV) surveillance of blood was mandated weekly until day +100 and subsequently with each clinic visit until day +180. Post-transplant iron chelation therapy could be resumed if indicated, after engraftment.

Outcomes

The primary endpoint was thalassemia-free survival (TFS) at 2 years. TFS was defined as survival without graft rejection and resumption of chronic erythrocyte transfusions. Graft rejection was defined as <20% donor chimerism evaluated by DNA analysis in myeloid cells. RBC chimerism was not evaluated. Overall survival (OS) was defined as the time from HSCT to last follow-up or death and thus reflected transplant-related mortality. Neutrophil recovery was defined as the first day of an absolute neutrophil count ≥ 500/μL for 3 consecutive days; platelet engraftment was a platelet count > 20,000/μL independent of platelet transfusions for 7 days.Engraftment was measured in peripheral blood–enriched myeloid/lymphoid cells by the amplification of genes containing short tandem repeats. Immune reconstitution was evaluated as recovery of lymphocyte subsets (CD3, CD4, CD8, CD16/56, and CD19 cells) calculated by flow cytometry and immunoglobulin levels at 6, 12, and 24 months post-HSCT.Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Sinusoidal obstructive syndrome was defined according to Seattle criteria [9]. Hematogenous and invasive infections were reported. Patients were followed on study for a minimum of 2 years post-HSCT and encouraged to enroll after on the Thalassemia Clinical Research Network Longitudinal Cohort Study (NCT00661804) for long-term follow-up subsequently.

Statistical Considerations

The study tested our hypothesis that this RIC regimen would be sufficient for donor cell engraftment and transfusion independence, with TFS ≥ 75%. Stopping rules included graft rejection, treatment-related mortality, or severe grade IV acute GVHD > 20%. TFS and OS were calculated using the Kaplan-Meier estimator and stratified by donor stem cell source. Continuous variables were summarized as median and range and categorical variables as percentages. Pesaro risk class was determined for all patients, but outcomes were not stratified by risk because of small numbers. The cumulative incidence method was used to estimate acute and chronic GVHD. In each case death was a competing risk. Immune reconstitution was determined by flow cytometry analysis of lymphocyte subsets and recovery of serum immunoglobulin levels in the absence of infusion. Statistical analysis was performed using GraphPad Prism 6.0 (GraphPad, La Jolla, CA).

RESULTS

Patient and Donor Characteristics

The study accrued patients from 14 centers nationwide. Donor and recipient characteristics are shown in Table 1. BM and UCB recipients were evenly distributed. β-Globin genotype