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Nonmyeloablative Stem Cell Transplantation with Alemtuzumab/Low-Dose Irradiation to Cure and Improve the Quality of Life of Adults with Sickle Cell Disease

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A B S T R A C T

Allogeneic hematopoietic stem cell transplantation (HSCT) is rarely performed in adult patients with sickle cell disease (SCD). We utilized the chemotherapy-free, alemtuzumab/total body irradiation 300 cGy regimen with sirolimus as post-transplantation immunosuppression in 13 high-risk SCD adult patients between November 2011 and June 2014. Patients received matched related donor (MRD) granulocyte colony–stimulating factor–mobilized peripheral blood stem cells, including 2 cases that were ABO incompatible. Quality-of-life (QoL) measurements were performed at different time points after HSCT. All 13 patients initially engrafted. A stable mixed donor/recipient chimerism was maintained in 12 patients (92%), whereas 1 patient not compliant with sirolimus experienced secondary graft failure. With a median follow-up of 22 months (range, 12 to 44 months) there was no mortality, no acute or chronic graft-versus-host disease (GVHD), and no grades 3 or 4 extramedullary toxicities. At 1 year after transplantation, patients with stable donor chimerism have normalized hemoglobin concentrations and improved cardiopulmonary and QoL parameters including bodily pain, general health, and vitality. In 4 patients, sirolimus was stopped without rejection or SCD-related complications. These results underscore the successful use of a chemotherapy-free regimen in MRD HSCT for high-risk adult SCD patients and demonstrates a high cure rate, absence of GVHD or mortality, and improvement in QoL including the applicability of this regimen in ABO mismatched cases (NCT number 01499888).

INTRODUCTION

Sickle cell disease (SCD) is often characterized by acute and chronic complications that progress with increasing age and negatively impact the patients' quality of life (QoL), lead to chronic morbidity, and result in high utilization of health care resources and reduced survival [1-3]. Allogeneic hematopoietic stem cell transplantation (HSCT) is the only curative option currently available for patients with SCD [4-7]. Previously, few studies had addressed the role of allogeneic HSCT in adult SCD patients, particularly those over 30 years of age [8]. In contrast, pediatric studies have shown encouraging results with HSCT using myeloablative [4-7]

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or reduced doses of chemotherapy in the conditioning regimen [9,10]. More recently, 2 studies have shown that nonmyeloablative regimens result in engraftment of HLA-matched related grafts in a high proportion of adult SCD patients without significant morbidity [11,12]. In the current study, we independently validate the unique experience of a chemotherapy-free allogeneic HSCT developed at the National Institutes of Health (NIH). We are the first to demonstrate the feasibility of this innovative regimen in ABO-mismatched recipients and report on its impact on QoL in adult SCD patients.

METHODS

Study Design and Eligibility

The primary endpoint of this prospective, phase I/II study (NCT number 01499888) was the engraftment rate at 1 year after HSCT. Secondary endpoints included transplantation-related toxicity, acute and chronic graft-versus-host disease (GVHD), SCD-related complications, QoL, and overall and disease-free survival. The protocol was approved by the University of Illinois at Chicago's institutional review board and written informed consent was obtained for all patients and donors in accordance with the Declaration of Helsinki.

Patients between the ages of 16 and 60 years with a diagnosis of SCD (genotypes Hb SS, Hb SC, Hb Sβ0-thalassemia, or Hb Sβ+-thalassemia) and complicated by 1 of the following were considered eligible for the study: (1) stroke, (2) ≥3 vaso-occlusive crises (VOC) per year requiring medical attention, (3) ≥2 life-time episodes of acute chest syndrome, (4) ≥2 episodes of priapism per year requiring medical attention, (5) red blood cell (RBC) alloimmunization during chronic transfusion therapy, (6) bilateral proliferative retinopathy with major visual impairment in at least 1 eye, (7) ≥2 joints with avascular necrosis, (8) chronic kidney disease, (9) stage I or II chronic lung disease, or (10) pulmonary hypertension defined as symptoms consistent with pulmonary hypertension and mean pulmonary artery pressure >25 mmHg. Additional eligibility requirements included having an HLA-identical matched related donor (MRD), being competent to sign informed consent, and having a Karnofsky score > 70, estimated glomerular filtration rate > 30 mL/min/1.73 m^2, left ventricular ejection fraction > 40%, and diffusing capacity of the lung for carbon monoxide > 50% predicted. Active hepatitis and a diagnosis of cirrhosis were exclusion criteria. The hematopoietic cell transplantation-specific comorbidity index (HCT-CI) was calculated from baseline data before HSCT as previously described [13].

Donors

Related donors were matched to the patients at the HLA-A, -B, -C, -DR, and -DQ loci by low-resolution molecular typing. Individuals with sickle cell trait were not excluded as donors. Donors received granulocyte colony–stimulating factor subcutaneously at a dose of 10 μg/kg/day to 12 μg/kg/day for 5 days followed by peripheral blood stem cell collection.

Transplantation Regimen

Patients underwent an RBC exchange transfusion using RBCs that were leukoreduced, irradiated, and matched for Rh, Kell, Kidd, Duffy, and MNS blood group antigens at day −10 with the goal of Hb S < 30%. Hydroxyurea was permanently discontinued at day −8 before stem cell infusion. Alemtuzumab (anti-CD52 monoclonal antibody) was administered intravenously as follows: .03 mg/kg on day −7, .1 mg/kg on day −6, and .3 mg/kg/day on days −5 to −3. Total body irradiation (TBI) was given as a single dose of 300 cGy on day −2. Immunosuppressive therapy with oral sirolimus was started on day −1. In addition to standard antimicrobial prophylaxis, patients received penicillin V potassium (250 mg twice daily) until pneumococcal vaccination was completed. Platelet transfusions were given for platelet counts $<50 \times 10^9$ cells/L. Standard engraftment criteria for neutrophils and platelets were followed and donor cell chimerism was measured in the whole blood and in circulating $CD3^+$ selected cells on days +30, +60, +90, +180, +365 and annually thereafter. Transthoracic echocardiograms and pulmonary function testing were performed before HSCT and 1 year after HSCT. Patients with T cell chimerism > 50% at day +365 were considered for sirolimus withdrawal.

QoL

Health-related QoL (HRQoL) was measured using short form (SF-36) v1 [14] at 4 time-points: before HSCT and at days +30, +90, and +365 after HSCT. Based on the patients' responses to the 36 items, scores were calculated for each of the 8 domains and normalized to the values of the United States' population (mean, 50; SD, 10) [15]. The SF-6D, which provides an overall utility score based on societal weights derived for items on the SF-36, was also calculated [16].

Statistical Analysis

Clinical and laboratory data are reported as median values (range). Continuous variables were compared using the paired *t*-test when appropriate using Systat 11 (Systat Software Corporation, San Jose, CA). Descriptive statistics were calculated for all HRQoL scores across different visits. HRQoL analyses were performed using repeated-measures ANOVA or the paired *t*-test. Standardized response means (SRM) were calculated at each visit as a measure of effect size and to evaluate the magnitude of change over time [17]. SRM was calculated as the ratio of the mean change score and the variability (standard deviation) of the change score for the group. Cohen's thresholds (.2 = small, .5 = medium, and .8 = large) were used to interpret the SRM scores [18]. Analysis of HRQoL data was restricted to patients who had completed the 1-year post-HSCT assessment.

RESULTS

Patient Characteristics

Between November 2011 and June 2014, 61 patients with SCD were referred for evaluation and 13 patients (Hb SS = 12, Hb SC = 1) between the ages of 17 and 40 years underwent allogeneic HSCT. Reasons for exclusion included lack of a suitable donor (n = 29), insurance denial (n = 11), or the patient declining further evaluation (n = 8). The characteristics of the 13 patients who underwent transplantation, including the indications for HSCT and the HCT-CI score, are shown in Table 1. Eight of the 13 patients were on hydroxyurea therapy for a minimum of 3 years before initiating the conditioning regimen. Twelve of the 13 patients had multiple SCD-related complications that met eligibility requirements. Four of the patients had RBC alloimmunization (median number of antibodies, 4; range, 2 to 7) and 2 patient-donor pairs were mismatched for the major ABO blood types (patient number 8: recipient A+, donor B+; patient number 13: recipient O+, donor A+). Granulocyte colony–stimulating factor–mobilized peripheral blood stem cells were collected from all 13 donors, including 4 with sickle cell trait, without complication. The median dose of $CD34^+$ cells transplanted was 8.2×10^6 $CD34^+$ cells/kg (range, 5.1 to 15.3×10^6 $CD34^+$ cells/kg).

Engraftment

Of the 13 patients, 11 had severe neutropenia ($<.5 \times 10^9$ neutrophils/dL) for a median duration of 6 days (range, 2 to 18 days) (Figure 1). Three patients had a platelet count that decreased to $<50 \times 10^9$ cells/L requiring platelet transfusions and 10 patients required RBC transfusions (median number of RBC units transfused, 1; range, 0 to 4) to maintain a hemoglobin between 9 g/dL and 10 g/dL. The median length of hospitalization was 33 days (range, 13 to 51 days). Donor cell chimerism at different time points is shown in Figure 2 and did not differ in patients who maintained a low (5 ng/mL to 10 ng/mL) versus high (10 ng/mL to 15 ng/mL) therapeutic serum level of sirolimus (data not shown). One patient who was noncompliant with sirolimus developed secondary loss of engraftment by day +90. At 1 year after HSCT, 12 of the 13 patients (92%) maintained stable donor chimerism (median whole blood chimerism, 81%; range, 31% to 98%; median $CD3^+$ chimerism, 43%; range, 10% to 86%) (Figure 2).

Transplantation-related Toxicity

Conditioning with alemtuzumab and low-dose TBI was generally well tolerated and no transplantation-related mortality was observed. Extramedullary toxicities > grade