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Allogeneic Hematopoietic Cell Transplantation Using Treosulfan-Based Conditioning for Treatment of Marrow Failure Disorders

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A B S T R A C T

Hematopoietic cell transplantation (HCT) is effective in the treatment of inherited marrow failure disorders and other nonmalignant diseases. Conventional myeloablative conditioning regimens have been associated with high transplant-related mortality, particularly in patients with comorbid conditions. Here we report on 14 patients with marrow failure disorders (Shwachman-Diamond syndrome, n = 3; Diamond Blackfan anemia, n = 4; GATA2 deficiency, n = 2; paroxysmal nocturnal hemoglobinuria, n = 4; and an undefined marrow failure disorder, n = 1) who underwent HCT on a prospective, phase II, multicenter clinical trial. Patients were given HLA-matched related (n = 2) or unrelated (n = 12) grafts after conditioning with treosulfan (42 g/m^2), fludarabine (150 mg/m^2), ± thymoglobulin (n = 11; 6 mg/kg). All patients engrafted. At a median follow-up of 3 years, 13 patients are alive with complete correction of their underlying disease. These results indicate that the combination of treosulfan, fludarabine, and thymoglobulin is effective at establishing donor engraftment with a low toxicity profile and excellent disease-free survival in patients with marrow failure disorders.

INTRODUCTION

Hematopoietic cell transplantation (HCT) offers curative treatment for cytopenias in patients with certain bone marrow failure disorders. In contrast to acquired aplastic anemia, some marrow failure disorders may be characterized by normocellular or even hypercellular marrow, which poses additional barriers to engraftment. As a result, these marrow failure disorders may require more aggressive conditioning to establish sustained donor engraftment. However, high-intensity myeloablative regimens are not well tolerated in many marrow failure disorders, and there is an increased risk for early transplant-related mortality from organ dysfunction or comorbidities associated with their underlying disease [1-4]. Therefore, less toxic conditioning approaches are needed.

In 2014 we reported the preliminary results of a US multicenter, prospective, phase II trial of a treosulfan-based reduced-intensity conditioning regimen for treatment of life-threatening nonmalignant disorders [5]. We observed a low incidence of both toxicity and transplant-related mortality, consistent with that reported in a number of large retrospective studies [6-10]. Several European groups have evaluated treosulfan in combination with fludarabine for conditioning of patients with primary immune deficiency disorders [7], hemophagocytic lymphohistiocytosis [8], and thalassemia [11,12]; however, limited data have been published regarding the use of treosulfan-based conditioning for patients with bone marrow failure disorders. Here we report on a cohort of patients with marrow failure disorders treated on a prospective US study.

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METHODS

Patients and Methods

Among 59 patients treated on protocol during the time frame for analysis, 14 had an underlying diagnosis of a marrow failure disorder, including Shwachman Diamond syndrome (SDS, n = 3), Diamond Blackfan anemia (DBA, n = 4), paroxysmal nocturnal hemoglobinuria (PNH, n = 4), GATA2 deficiency (n = 2), and an undefined marrow failure disorder (n = 1). Toxicity and survival data on 8 of the 14 patients with marrow failure were reported previously [5]. The protocol was approved by the Institutional Review Boards of all participating institutions and monitored by an independent Data Safety Monitoring Board. Patients or their legal guardians provided written consent.

The conditioning regimen consisted of treosulfan 14 g/m^2 given once daily i.v. on days –6 through –4 (total dose 42 g/m^2) and fludarabine 30 mg/m^2 given once daily i.v. on days –6 through –2 (total dose 150 mg/m^2), as previously reported [5]. Patients were given either marrow or granulocyte colony-stimulating factor (G-CSF) mobilized peripheral blood stem cell grafts. Prophylaxis for graft-versus-host disease (GVHD) included tacrolimus and methotrexate. Tacrolimus was started as an i.v. continuous infusion on day –1 at a dose of .03 mg/kg and was continued until at least day +50 post-HCT followed by a taper of approximately 5% per week if there was no evidence of GVHD and the patient's graft was stable. Methotrexate was given on day +1 (15 mg/m^2/dose) and on days +3, +6, and +11 (10 mg/m^2/dose). After the first 3 patients, thymoglobulin (rabbit antithymocyte globulin [rATG]) was added to the regimen and given once daily i.v. on days –4 through –2 (total dose 6 mg/kg; n = 11) [13,14]. Supportive care included antibiotic prophylaxis, i.v. immunoglobulin, nutritional support, and weekly PCR monitoring for reactivation of cytomegalovirus, Epstein-Barr virus, and adenovirus, according to institutional practices.

The pre-HCT comorbidity score was assessed by the augmented HCT-specific comorbidity index [15-17]. Diagnosis, clinical grading, and treatment of acute and chronic GVHD were performed according to established criteria [18,19]. Toxicities were defined by the National Cancer Institute's Common Toxicity Criteria, version 2.0, excluding hematologic toxicities [20]. Disease response was evaluated by hematopoietic recovery, which was assessed by peripheral blood counts, transfusion independence, and bone marrow evaluation. In addition, flow cytometry of peripheral blood for glycosylphosphatidylinositol–anchored extracellular proteins was used to assess PNH. Donor chimerism levels were assessed in flow cytometry sorted CD33$^+$, CD3$^+$, CD19$^+$, and CD56$^+$ subsets by PCR-based analyses of polymorphic microsatellite regions, using methods previously described [21-24]. Primary neutrophil engraftment was defined as absolute neutrophil count $\geq .5 \times 10^9$/L for 3 consecutive days. The median time to platelet recovery was defined as $>50 \times 10^9$/L for 5 days.

The method of Kaplan and Meier was used to estimate overall survival, which was defined as the duration from date of transplant to date of death due to any cause. Patients last known to be alive were censored at their date of last contact. Graphic representations of donor chimerism values across time were created by taking the chimerism value closest to day 28, day 80, day 180, and yearly thereafter up to 5 years after HCT. These values are depicted in the figures as occurring at these time points even though individual chimerism values may have occurred at times earlier or later than the listed time.

RESULTS

Patient Characteristics

Between June 2010 and October 2016, 14 patients with an underlying diagnosis of bone marrow failure underwent HCT. Patient characteristics at the time of HCT are shown in Tables 1, 2, 3, and 4. The median age at HCT was 15 years (range, 2 to 22). The median augmented HCT-specific comorbidity index was 1 (range, 0 to 8). None of the patients had significant underlying cardiac or renal dysfunction pre-HCT. Three patients had underlying pulmonary disease defined as a forced expiratory volume in 1 second (FEV1) or diffusing capacity of the lung for carbon monoxide (DLCO) 66% to 80% (n = 1; SDS) or an FEV1 or DLCO ≤65% (n = 2; DBA and PNH). In addition, 1 patient with PNH (patient 9) had mild transaminitis pre-HCT [alanine aminotransferase (ALT) 2.5× the upper limit of normal]. This patient had received a previous HLA-matched unrelated peripheral blood stem cell HCT after nonmyeloablative conditioning; however, this patient developed recurrent hemolysis and cytopenias roughly 1 year after the first HCT consistent with either recurrent PNH or a dysregulated immune system, prompting a second HCT on the current trial.

Engraftment and Chimerism

Neutrophil engraftment was observed in all patients at a median of 21 days (range, 15 to 26). The median time to platelet recovery was 28 days (range, 10 to 76). The median number of RBC and platelet transfusions was 3 (range, 0 to 10) and 6 (range, 1 to 28), respectively. Full donor chimerism, defined as ≥95% donor cell origin of peripheral blood CD3$^+$ T cell and CD33$^+$ myeloid subsets, was established in 13 patients, and mixed donor-host chimerism was present in 1 (patient 5; Tables 1, 2, 3, and 4 and Figure 1).

Transplant-Related Complications

All patients were observed for nonhematologic toxicities possibly related to the conditioning regimen through day 30 post-HCT. Similar to the previous report, there were few clinically significant toxicities. Of the 14 patients enrolled, 5 developed 1 or more toxicities that included grade 3 mucositis (n = 4); grade 3 skin rash not attributable to infection or GVHD (n = 1); grade 3 hypoxia, which was transient in the setting of respiratory syncytial virus (RSV) infection (n = 1); grade 3 pancreatitis, which resolved (n = 1); and grade 4 allergic reaction to rATG, which resolved after discontinuation of rATG after the first dose (n = 1). None of the patients developed liver toxicity, including the 6 patients with a pre-HCT diagnosis of iron overload (patients 4, 5, 6, 7, 12, and 14). None of the patients developed cardiac or renal toxicity.

Six patients developed grade II acute GVHD, and 1 patient who did not receive rATG developed grade IV acute GVHD. Two patients developed delayed acute skin GVHD at days +161 and +175 post-HCT, and 2 patients developed chronic GVHD by National Institutes of Health consensus criteria. Eleven patients have successfully tapered off immune suppression at a median of 347 days (range, 160 to 1432) post-HCT. Two patients remain on immune suppression at 3 and 6 months post-HCT, and 1 patient died on immune suppression.

All patients were monitored weekly by PCR for viral reactivation. Epstein-Barr virus reactivation was detected in 3 patients; all resolved completely after rituximab therapy. Cytomegalovirus reactivation was detected in 1 of the 4 patients who had positive cytomegalovirus serology pre-HCT. In addition, 1 patient had human herpes virus 6 (HHV6) reactivation that resolved after foscarnet therapy. Other infections within the first 100 days after HCT included RSV upper respiratory infection on day +5 (n = 1), central line–associated bacteremia (n = 3), and *Clostridium difficile* enteritis (n = 3), all resolving with therapy.

Survival and Disease Response

With a median follow-up of 3 years (range, .3 to 6.5), 13 of the 14 patients are alive (Figure 2) with restoration of normal marrow function and Lansky/Karnofsky performance scores of 100% at last follow-up. One patient (patient 9) died of grade IV GVHD on day +158; this patient did not receive rATG. Disease responses at last follow-up are shown in Tables 1, 2, 3, and 4.

SDS: patients 1, 2, and 3

All 3 patients had 100% donor multilineage engraftment 5.5, 4.6, and 3.1 years, respectively, after HCT. All 3 patients were transfusion independent with resolution of neutropenia (patients 1, 2, and 3), anemia (patients 2 and 3), and thrombocytopenia (patients 1, 2, and 3) post-HCT. Patient 3