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

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Abstract

Hematopoietic cell transplantation (HCT) is effective in the treatment of inherited marrow failure disorders and other non-malignant diseases. Conventional myeloablative conditioning regimens have been associated with high transplant related mortality particularly in patients with co-morbid 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 multi-center clinical trial. Patients were given HLA-matched related (n=2) or unrelated (n=12) grafts following conditioning with treosulfan (42 grams/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.

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Conflicts of Interest Statement

This study was supported in part by research funding from Medac GmbH (Hamburg, Germany), which also provided treosulfan. In addition, medac GmbH covered travel costs for meetings. Otherwise, the author have no further conflicts of interest in relation to this work.

Author Contributions

L.M.B. and A.E.W. designed the study, analyzed the data and wrote the manuscript. L.M.B., A.S., J.A.T., J.D., and A.E.W. performed the research. A.S., J.A.T., J.D., C.D., H.F., D.M., K.S.B., A.G., K.M., B.M.S., H.J.D., and R.S. critically reviewed the manuscript.

Keywords

one marrow failure; Diamond Blackfan Anemia; Shwachman-Diamond Syndrome; reduced toxicity conditioning in nonmalignant diseases

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 (TRM) 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 U.S. multicenter prospective phase I/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 TRM, 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 U.S. study.

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 (DSMB). Patients or their legal guardians provided written consent. The conditioning regimen consisted of treosulfan 14 g/m^2 given once daily IV on days −6 through −4 (total dose 42 g/m^2) and fludarabine 30 mg/m^2 given once daily IV 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 mobilized peripheral blood stem cell (PBSC) grafts. Prophylaxis for graft-vs.-host disease (GVHD) included tacrolimus and methotrexate. Tacrolimus was started as an intravenous (IV) continuous infusion on day −1 at a dose of

0.03 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 anti-thymocyte globulin, rATG) was added to the regimen and given once daily IV on days −4 through −2 (total dose 6 mg/kg; n=11)[13, 14]. Supportive care included antibiotic prophylaxis, intravenous immunoglobulin, nutritional support, and weekly polymerase chain reaction (PCR) monitoring for reactivation of cytomegalovirus (CMV), Epstein-Barr virus (EBV), and adenovirus, according to institutional practices.

The pre-HCT co-morbidity score was assessed by the augmented HCT co-morbidity index (HCT-CI) [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 glycosylphosphatidyl inositol (GPI)-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 ≥ 0.5 × 10^9/L for 3 consecutive days. The median time to platelet recovery was defined as >50 × 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. Graphical 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 following 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 (range 2–22) years. The median augmented HCT-CI was 1 (range 0–8). None of the patients had significant underlying cardiac or renal dysfunction pre-HCT. Three patients had underlying pulmonary disease defined as an FEV1 or DLCO 66%-80% (n=1; SDS) or an FEV1 or DLCO ≤65% (n=2; DBA and PNH). In addition, one patient with PNH (patient #9) had mild transaminitis pre-HCT (ALT 2.5 × the upper limit of normal). This patient had received a previous HLA-matched unrelated PBSC HCT following nonmyeloablative conditioning; however, this patient developed recurrent hemolysis and cytopenias roughly 1 year following 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 (range, 15–26) days. The median time to platelet recovery was 28 (range, 10–76) days. The median number of red blood cell (RBC) and platelet transfusions was 3 (range, 0–10), and 6 (range, 1–28), 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 non-hematologic 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 one 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 RSV infection (n=1), grade 3 pancreatitis which resolved (n=1), and grade 4 allergic reaction to rATG which resolved following 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 (patient #4, #5, #6, #7, #12, and #14). None of the patients developed cardiac or renal toxicity.

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

All patients were monitored weekly by PCR for viral reactivation. EBV reactivation was detected in 3 patients; all resolved completely after rituximab therapy. CMV reactivation was detected in 1 of the 4 patients who had positive CMV serology pre-HCT. In addition, one patient had 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 (range 0.3–6.5) years, 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 (#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.

Shwachman Diamond syndrome (SDS, patients #1, #2, and #3)—All three patients have 100% donor multi-lineage engraftment 5.5, 4.6, and 3.1 years, respectively following HCT. All three patients are transfusion independent with resolution of neutropenia (patient #1, #2, and #3), anemia (patient #2 and #3) and thrombocytopenia (patient #1, #2, and #3) post-HCT. Patient #3 had a history of 17p deletion by cytogenetics and FISH pre-HCT. Follow-up marrow evaluation at 1-year post-HCT showed no evidence of 17p deletion by cytogenetics and FISH evaluations.

Diamond Blackfan anemia (DBA, patients #4, #5, #6, and #7)—Of the three patients with >1 year of follow-up (patients #4, #5, and #6), all have normal hemoglobin levels and are transfusion independent 4.5, 4.0, and 3.0 years, respectively post-HCT, including patient #5 who has mixed donor-recipient chimerism. In addition, patient #6 also had resolution of thrombocytopenia. Patient #7 is currently 3 months post-HCT and is transfusion independent with normal hemoglobin levels and resolution of neutropenia.

Before HCT, all patients with DBA had a history of iron overload with either elevated serum ferritin levels or increased hepatic iron on T2* MRI (Table 2). In addition, three patients (patients #4, #6, and #7) were receiving iron chelation therapy pre-HCT. Post-HCT one patient underwent phlebotomy × 18 months with improvement of liver iron to near normal (patient #6). One patient remains on iron chelation therapy post-HCT (patient #4). This patient required transfusions post-HCT due to autoimmune hemolytic anemia. Patient #7 is currently 3 months post-HCT with a serum ferritin of 1690 ng/mL.

Paroxysmal nocturnal hemoglobinuria (PNH, patients #8, #9, #10, and #11)—Of the four patients with PNH, one (#11) received eculizumab for PNH therapy pre-HCT. This patient had a history of debilitating fatigue and continued hemolysis despite 11 months of eculizumab therapy which prompted HCT. The patient continued on eculizumab therapy post-HCT until donor engraftment was confirmed and PNH cells declined to <1%. An additional patient (#10) was started on Eculizumab 3 days prior to the start of conditioning and continued eculizumab through engraftment. Three of the 4 patients are alive 6.5, 2.3, and 1.4 years post-HCT. One patient (#9) died of grade IV gut GVHD on day +158; this patient did not receive rATG. The three living patients all achieved full donor CD3 and CD33 engraftment and had resolution of PNH with normalization of blood counts and normal expression of glycosylphosphatidyl inositol-anchored proteins (Table 3).

GATA 2 deficiency—Patient #12 had a 4-year history of pancytopenia and mild immune dysfunction (Table 4). Genetic testing identified a heterozygous mutation in the *GATA2* gene (c.1082G>A/G, p.R361H) approximately 6 months before HCT. The bone marrow showed trisomy 8 in 1.6% of marrow cells, without evidence for myelodysplasia. There was evidence for mild immune dysfunction, with low peripheral blood T and B lymphocyte subsets, but normal lymphocyte function and immunoglobulin production. Immunophenotyping showed B-cell lymphopenia with B cells constituting only 1.8% of the lymphocyte population. There were virtually no immature B cells observed; however, mature-naïve and mature-memory cells were present. Despite the low B cell number, immunoglobulin class-switching appeared normal in the memory cell population and there were both IgG+ and IgA+ switched memory B cells present. BAFF receptor expression was decreased relative to healthy controls, which was likely due to B cell lymphopenia. Post-HCT, the patient achieved full donor multi-lineage engraftment with resolution of anemia, thrombocytopenia, and neutropenia, and normalization of peripheral blood T and B lymphocyte subsets. The bone marrow evaluations at 3 and 12 months post-HCT showed no evidence of trisomy 8. Patient #13 had a 3-year history of progressive neutropenia, mild anemia and thrombocytopenia. An extensive marrow failure work-up was performed that identified a heterozygous mutation in the GATA2 gene (c.1072_1074delACC, p.T358del). This patient also had evidence for mild immune dysfunction, with low peripheral blood T and B lymphocyte subsets and had a history of viral warts pre-HCT. The patient is currently 6 months post-HCT with full donor CD3 and CD33 engraftment and has resolution of neutropenia and thrombocytopenia. This patient continues to have mild anemia.

Undefined marrow failure disorder—Patient #14 was diagnosed with bone marrow failure characterized by neutropenia, thrombocytopenia, macrocytic anemia, and a marrow that was hypocellular for age (cellularity 40%). The patient had no physical anomalies or family history to suggest a genetic disorder. Despite a comprehensive evaluation, no causative genetic mutation could be identified. Post-HCT, full donor chimerism was achieved, resulting in complete resolution of all cytopenias, and transfusion independence. This patient had evidence of iron overload pre-HCT based on a serum ferritin of 550 ng/mL and a hepatic T2* MRI that showed the liver iron content to be elevated at 9.1–10.1 mg Iron/g dry weight. This patient underwent monthly phlebotomy × 3 months post-HCT which resulted in improvement in his serum ferritin to 351 ng/mL as well as decreased hepatic liver iron content to 4.7–4.8 mg iron/g dry weight.

DISCUSSION

Bone marrow failure disorders are rare diseases that pose a challenge for successful HCT, as many patients have pre-existing organ dysfunction that increases the risk for mortality with conventional conditioning agents. Yet in many cases myeloablative conditioning is required to eliminate the abnormal marrow and facilitate sustained donor engraftment; thus there is a significant need to develop less toxic, yet myeloablative regimens. Treosulfan is a pro-drug of an alkylating agent structurally related to busulfan, and has similar myelosuppressive and immunosuppressive properties [20]. However, treosulfan has a different mode of alkylation, is not activated by liver enzymes, and has highly predictable pharmacokinetics. These properties reduce its potential for causing liver toxicity, as well as other tissue damage. We and others have successfully used a treosulfan-based regimen in an effort to reduce the risk for toxicity and mortality associated with allogeneic HCT for treatment of nonmalignant disorders [5]. Here we show that when combined with fludarabine and rATG, a treosulfan-containing regimen is well tolerated and can be highly effective in correcting marrow failure disorders.

Historical experience with conventional myeloablative conditioning regimens for patients with SDS has shown event-free survival to be around 60% [4]. The poor outcome can be partially explained by a delay of HCT until patients developed myelodysplastic syndromes (MDS), in which case mortality from relapse contributed to poor survival. However, patients without MDS also have a high transplant related mortality. Patients with SDS may develop cardiac dysfunction that may not be detected by echocardiogram [25–27], and may explain the increased incidence of cardiac failure after HCT with conventional regimens [1, 4]. Liver failure also has been reported following conventional HCT. Several case series have shown promising results with reduced intensity regimens, including fludarabine, melphalan, and alemtuzumab for HLA-matched grafts, with the main transplant-related complication being infections [28]. Sauer, et al. reported successful outcome in 2 of 3 patients conditioned with treosulfan in combination with fludarabine, melphalan, and alemtuzumab or rATG [29]. Taken together with our results, these studies show very low risk of mortality with reduced intensity regimens and support the use of HCT early after onset of marrow failure or detection of high-risk cytogenetics associated with a progression to MDS, particularly when an HLA matched related or unrelated donor is available. In contrast to SDS, patients with DBA appear to have better outcome with conventional conditioning regimens. The largest series of DBA patients was reported by the Center for International Blood and Marrow Transplant, and included 61 patients with about half of the cohort receiving HLA-matched sibling donor grafts. Most patients were conditioned with cyclophosphamide combined with either busulfan or total body irradiation. Patients who received HLA matched sibling grafts and those with performance scores 90–100 had significantly superior survival at 100 days, 1 year, and 3 years post HCT, approaching 80%. Given the larger experience in patients with other nonmalignant diseases showing very low mortality, further studies of treosulfan-based conditioning in patients with DBA are warranted to determine if equivalent or better survival can be achieved without the potential late effects of busulfan and TBI, such as growth retardation, gonadal toxicity, or secondary malignancies [30–34].

PNH is another rare marrow failure disorder for which HCT is indicated when medical therapy fails to control the disease manifestations. HCT is performed most often for the aplastic phase of PNH, in which case traditional nonmyeloablative regimens are quite successful [35–39]. Our institutional experience in adult patients with PNH showed that nonmyeloablative conditioning was effective in establishing donor engraftment in patients with either marrow aplasia or normocellular marrows [37]; however, G-CSF mobilized peripheral blood stem cells were given, and most of the patients developed GVHD. Conditioning with treosulfan, fludarabine, and rATG, followed by an allogeneic marrow graft, may be an acceptable alternative, particularly for patients with normal marrow cellularity. The two patients treated with eculizumab before HCT were maintained on it through conditioning until documented clearance of the PNH clone, without additional toxicity.

GATA2 deficiency caused by mutations in the *GATA2* gene is a more recently described cause of bone marrow failure. In addition to bone marrow failure, patients with GATA2 deficiency can have underlying immune defects and are at risk for developing MDS or acute myelogenous leukemia (AML) [40–42]. Allogeneic HCT is a potentially curative therapy; however, patients often have significant underlying comorbidities that increase the risk of transplant related toxicities and mortality. Grossman et al. reported on 14 patients with GATA2 deficiency who underwent allogenic HCT following nonmyeloablative conditioning consisting of low dose TBI (2 Gy), fludarabine, +/− cyclophosphamide depending on the stem cell source [PBSC (n=8), bone marrow (n=2), or cord blood (n=4)] [42]. The majority of patients had MDS (<5% blasts) at the time of HCT. Six of the 14 patients died from rejection (n=2), infections (n=2), or other causes (n=2). Although HCT using nonmyeloablative conditioning was effective at correcting the underlying hematologic, immunologic and clinical manifestations of GATA2 deficiency, the authors stated that they are currently investigating a more intensive conditioning regimen consisting of busulfan and fludarabine with the goal of decreasing the risk of rejection and relapse. Our results as well as other published studies using treosulfan-based conditioning for patients with MDS/AML support that treosulfan-based conditioning may be another viable option for patients with GATA2 deficiency [43–45].

As previously reported, the initial patients on the prospective trial were conditioned with treosulfan and fludarabine alone. Subsequently, rATG was added to the regimen to reduce the incidence of grades III-IV acute GVHD [5], decreasing the incidence of acute grades III-IV GVHD from 33% to 0%. In the current cohort of 14 patients with marrow failure, only three patients did not receive rATG and one died of grade IV GVHD. Of the 11 patients who received rATG, none developed grades III-IV GVHD, and none died from infectious complications.

We were interested in determining the extent of disease response according to the level of donor chimerism established in each patient. However, all but one patient achieved full donor chimerism, defined as >95% donor cells in both CD3+ and CD33+ subsets. Disease response in the single case of DBA with <95% donor CD33 cells was similar to patients with full chimerism. Thus, the combination of treosulfan with fludarabine and rATG appears to be effective in establishing donor chimerism. The ability to establish full donor chimerism with minimal toxicity is particularly important in those patients with bone marrow failure disorders who have cytogenetic abnormalities with a risk for transformation to leukemia. In summary, the combination of treosulfan, fludarabine, and rATG appears promising as a conditioning regimen for patients with bone marrow failures disorders, which resulted in excellent long-term disease-free survival.

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HIGHLIGHTS

- Treosulfan-based conditioning has a low toxicity profile
- High level donor engraftment in marrow failure disorders
- Excellent disease-free survival

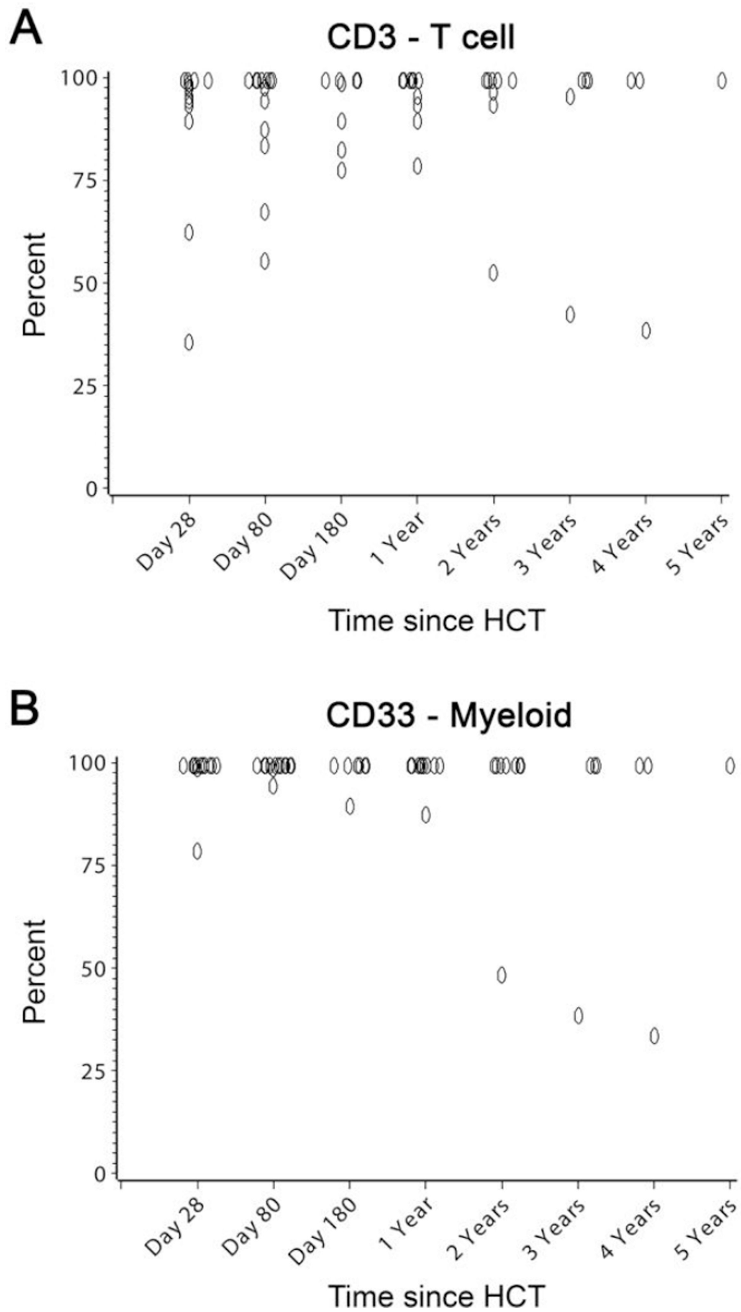

Figure 1. CD3+ and CD33+ donor chimerism in 14 patients conditioned with treosulfan-based conditioning

Shown are the percent donor chimerism of sorted peripheral blood CD3+ (panel **A**) and CD33+ (panel **B**) subsets according to day after transplant. Overlapping points at days +28, +80, +180, years, and at 100% chimerism, are jittered slightly to improve visibility.

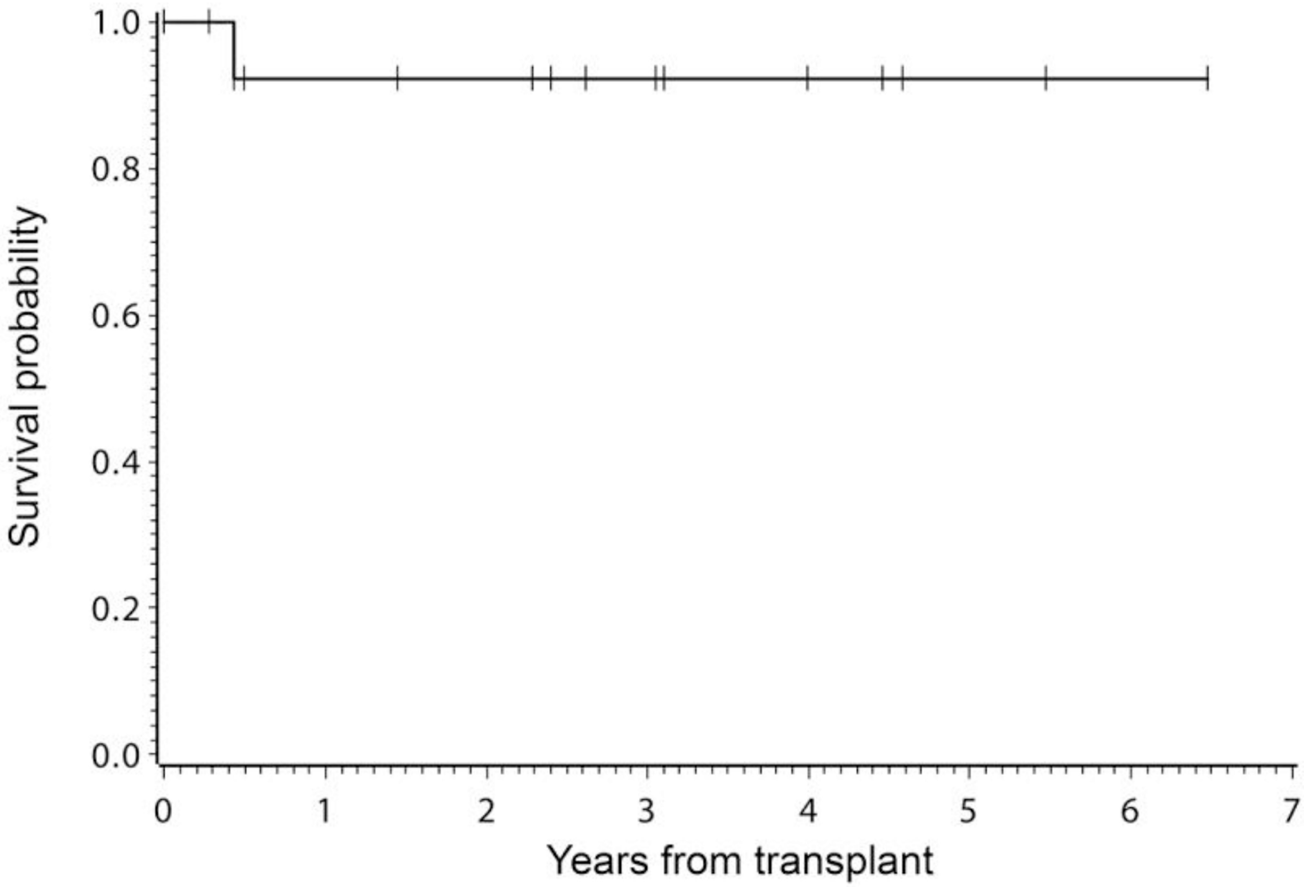

Figure 2. Disease-free survival

Shown is the Kaplan Meir estimate of disease-free survival for 14 patients with bone marrow failure disorders who received treosulfan-based conditioning.

Table 1

Shwachman Diamond syndrome

PRE-HCT CHARACTERISTICS	**PATIENT #1**	**PATIENT #2**	**PATIENT #3**
Age at diagnosis /at HCT (yr)	12 / 19.4	6 / 7.2	0.6 / 2.8
Patient sex	Male	Female	Male
Genetic mutation	*SBDS* compound heterozygous: c. 183_184TA>CT; c. 258+2T>C (splicing)	*SBDS* compound heterozygous: c. 258+2T>C (splicing); c. 624+1G>A (splicing)	*SBDS* compound heterozygous: c. 183_184TA>CT; c.258+2T>C (splicing)
Pancreatic dysfunction	Yes	Yes	Yes
Trypsinogen ng/mL	11.0 (LLN 16.9)	8.9 (LLN 10)	5.4 (LLN 10)
Isoamylase (normal >13 U/L)	3	5	3
Additional clinical features	–	Cleft-palate, Pierre Robin, Height <5%ile	Height 5–10%ile
Augmented HCT/CI at HCT	3	1	1
Peripheral blood counts			
ANC (cells/µ.L)	600	170	180
Hematocrit	39%	19%	20%
Platelet Count (cells/µL)	58,000	7,000	76,000
Transfusion dependent	No	Yes (pRBC and platelets)	Yes (pRBCs)
Bone marrow evaluation			
Cellularity	Average 7–10%	Average 60%	Average 50%
Cytogenetics/FISH	Normal at HCT/h/o deletion 20q	Normal/Normal	+1,der(1;17)(q10;q10)[17]/17p- (33.8%)
Indication(s) for HCT	Cytopenias	Cytopenias, pRBC and platelet transfusion dependent	Cytopenias, pRBC transfusion dependent, abnormal FISH
HCT Characteristics and Outcomes			
Donor/stem cell source	MURD/marrow	MURD/PBSC	MURD/marrow
Follow-up (yr)	Alive, 5.5	Alive, 4.6	Alive, 3.1
Donor chimerism (CD3+/CD33+)[†]	100%/100%	100%/100%	100%/100%
GVHD[§]			
Acute/Chronic (Yes/No)	No/No	Yes/No	Yes/No
Day Immune Suppression Stopped	242	278	450
Peripheral blood counts[†]			
ANC (cells/µL)	4473	2090	1460
Hematocrit	48.3%	39.4%	37.4%
Platelet count (cells/µL)	159,000	206,000	272,000
Bone marrow evaluation[†]			
Cellularity	20%	70%	N/A
Cytogenetics/FISH	Normal/Normal	Normal/ND	Normal/Normal

PRE-HCT CHARACTERISTICS	**PATIENT #1**	**PATIENT #2**	**PATIENT #3**
Disease response	Normal blood counts, Transfusion Independent	Normal blood counts, Transfusion Independent	Normal blood counts, Transfusion Independent, Normal marrow cytogenetics

† At last time point studied;

§ Acute grade II-IV GVHD, delayed acute GVHD, or NIH chronic GVHD

Abbreviations: ANC, absolute neutrophil count; HCT, hematopoietic cell transplantation; HCT-CI, hematopoietic cell transplantation comorbidity index; h/o, history of; MURD, matched unrelated donor; N/A, not available; ND, not done; PBSC, peripheral blood stem cells; pRBC, packed red blood cell; R, recipient; SDS, Shwachman-Diamond syndrome; yr, years

Table 2

Diamond Blackfan anemia

PRE-HCT CHARACTERISTICS	PATIENT #4	PATIENT #5	PATIENT #6	PATIENT #7
Age at diagnosis/at HCT (yr)	0.3 / 6.1	1.2 / 12.2	0.1 / 21.9	0.1 / 2.3
Patient sex	Male	Female	Female	Female
Genetic mutation	None	None	None	*RPS19* Heterozygous: c357-2A>G (splicing)
Failed steroids	Yes	Initial steroid response, 10 yr remission	Yes	Yes
Clinical features	Autism, Neonatal intracerebral hemorrhage, GH deficiency, Hypogonadotropic hypogonadism, Bicuspid aortic valve	–	Hypothyroidism, Bicuspid aortic valve	Anterior ectopic anus
Iron				
Ferritin ng/mL	342	674	1643	1215
T2* MRI[‡]	Hepatic: 3.36 Myocardial: 16.4	Hepatic: 10.3 Myocardial: ND	Hepatic: 9.7 Myocardial: 41	Hepatic: 1.9 Myocardial: 45–69
Liver biopsy	Slight to moderate hemosiderosis, septal fibrosis (Batts & Ludwig, grade 2–3, stage 3)	None	4+ iron, mild to moderate portal fibrosis	None
Augmented HCT/CI	1	0	5	0
Peripheral blood counts				
ANC (cells/μL)	960	2540	2440	430
Hematocrit	23%	25%	24%	24%
Platelet count (cells/μL)	180,000	382,000	60,000	238,000
Transfusion dependent	Yes (pRBC)	Yes (pRBC)	Yes (pRBC)	Yes (pRBC)
Bone marrow evaluation				
Morphology	Marked erythroid hypoplasia, slight myelofibrosis	Moderate erythroid hypoplasia, mild erythroid atypia	Erythroid aplasia, no dysplasia	Erythroid aplasia, no dysplasia
Cellularity	85%	60–70%	20–30%	40%
Cytogenetics	Normal	Normal	Normal	Normal
Indication for HCT	pRBC transfusion dependent, iron overload (on Exjade and desferol)	pRBC transfusion dependent	pRBC transfusion dependent, iron overload (on Exjade)	pRBC transfusion dependent, iron overload (on Exjade and desferol), Neutropenic despite G-CSF, frequent infections
HCT Characteristics and Outcomes				
Donor/Stem cell source	MURD/marrow	MURD/marrow	MURD/marrow	MURD/marrow
Follow-up (yr)	Alive, 4.5	Alive, 4.0	Alive, 3.0	Alive, 0.3
Donor chimerism (CD3+/CD33+)[†]	100%/100%	39%/34%	96%/100%	100%/100%
GVHD[§]				
Acute/Chronic (Yes/No)	Yes/Yes	Yes/No	No/No	Yes/No

PRE-HCT CHARACTERISTICS	PATIENT #4	PATIENT #5	PATIENT #6	PATIENT #7
Day Immune Suppression Stopped	1432	392	198	Still on
Peripheral blood counts†				
ANC (cells/μL)	14,421	4570	4770	7280
Hematocrit	34.9%	39%	42%	37%
Platelet count (cells/μL)	336,000	187,000	215,000	82,000
Bone marrow evaluation†				
Morphology / cellularity	Trilineage hematopoiesis, 30–40%	ND/ND	ND/ND	N/A/N/A
Cytogenetics	Normal	ND	ND	Normal
Disease response	Normal hemoglobin, Transfusion independent	Normal hemoglobin, Transfusion independent	Normal hemoglobin, Transfusion independent	Normal hemoglobin, Transfusion independent, Resolution of neutropenia

†at last time point studied;

‡Hepatic T2* mg Iron/g dry weight hepatic tissue, Myocardial T2*: msec;

§Acute grade II-IV GVHD, delayed acute GVHD or NIH chronic GVHD

Abbreviations: ANC, absolute neutrophil count; DBA, Diamond-Blackfan anemia; GH deficiency, growth hormone deficiency; HCT, hematopoietic cell transplantation; HCT-CI, hematopoietic cell transplantation comorbidity index; MURD, matched unrelated donor; N/A, not available; ND, not done; pRBC, packed red blood cell; R, recipient; vs, versus; yr, years

Table 3

Paroxysmal nocturnal hemoglobinuria

PRE-HCT CHARACTERISTICS	**PATIENT #8**	**PATIENT #9**	**PATIENT #10**	**PATIENT #11**
Age at diagnosis/ at HCT (yr)	15.4 / 15.9	19 / 22.1	14.5 / 17.6	14 / 14.9
Patient sex	Female	Female	Female	Male
GP-1 flow cytometry	GP1-deficient neutrophils (57–60%), monocytes (62%), erythrocytes (1%)	Normal post 1st-HCT	GP1-deficient neutrophils (82%), monocytes (79.2%), and erythrocytes (5.7%)	GP1-deficient neutrophils (27.7%), monocytes (77.6%), and erythrocytes (54.1%)
History of eculizumab	NO	NO	Yes; initiated 3 days prior to start of conditioning and continued through engraftment	Yes; initiated 11 months prior to HCT and continued through engraftment
Augmented HCT/CI	1	8	1	0
Peripheral blood counts				
ANC (cells/μL)	720	700	380	560
Hematocrit	25%	23%	22%	32%
Platelet count (cells/μL)	13,000	33,000	13,000	179,000
Transfusion dependent	Yes (pRBCs and platelets)	Yes (pRBCs and platelets)	Yes (pRBCs and platelets)	No
Bone marrow evaluation				
Cellularity	10%-20%	70%	70%	70%
Cytogenetics	Normal	Normal	Normal	Normal
Indication for HCT	Cytopenias, G-CSF dependent, pRBC and platelet transfusion dependent	Cytopenias following 1st HCT, pRBC and platelet transfusion dependent.	Cytopenias, pRBC and platelet transfusion dependent	Failed Eculizumab (profound fatigue, continued hemolysis)
HCT Characteristics and Outcomes				
Donor/Stem cell source	MURD/PBSC	MURD/marrow	A-Allele MMURD/PBSC	MRD/BM
Follow-up (yr)	Alive, 6.5	Died GVHD, 0.4	Alive, 2.3	Alive, 1.4
Donor Chimerism (CD3+/CD33+)†	100%/100%	100%/100%	97%/100%	95%/100%
GVHD§				
Acute/Chronic (Yes/No)	No/No	Yes/No	No/Yes	No/No
Day Immune Suppression Stopped	160	Died on	423	513
Peripheral blood counts†				
ANC (cells/μL)	3300	3965	4400	3460
Hematocrit	40.9%	27.9%	34.5%	42%
Platelet Count (cells/μL)	289,000	53,000	275,000	231,000
Bone marrow evaluation†				
Cellularity	N/A	20%	70%	50%
Cytogenetics	Normal	Normal	Normal	Normal
Disease response	Normal GP-1 expression	Normal GP-1 expression	Normal GP-1 expression	Normal GP-1 expression

† at time point last studied

§Acute grade II-IV GVHD, delayed acute GVHD or NIH chronic GVHD

Abbreviations: HCT, hematopoietic cell transplantation; HCT-CI, hematopoietic cell transplantation comorbidity index; MRD, matched related donor; MURD, matched unrelated donor; MM, mismatched; N/A, not available; PBSC, peripheral blood stem cells; pRBC, packed red blood cell; R, recipient; yr, years

Table 4

GATA2 deficiency and undefined bone marrow failure

PRE-HCT CHARACTERISTICS	**PATIENT #12**	**PATIENT #13**	**PATIENT #14**
Age at diagnosis/at HCT (yr)	12.5 / 16.8	11.4 / 15.1	4.7 / 5.6
Patient sex	Female	Male	Male
Genetic mutation	*GATA2* Heterozygous: c. 1082G>A/G (p.R361H)	*GATA2* Heterozygous: c. 1072_1074delACC (p.T358del)	None
Clinical features	Hashimoto's thyroiditis, primary EBV	Viral warts	–
Iron			
Ferritin ng/mL	929	42	550
T2* MRI[‡]	Hepatic: 5.11 Myocardial: 36.39	ND	Hepatic: 9.1–10.1 Myocardial: 33.7–34.2
Augmented HCT/CI	1	0	1
Peripheral blood counts			
ANC (cells/μL)	470	187	250
Hematocrit	22%	33.8%	25%
Platelet count (cells/μL)	87,000	105,000	16,000
Transfusion dependent	Yes (pRBC)	No	Yes (pRBC and platelets)
Bone marrow evaluation			
Cellularity	Average 40%	Average 40–50%	40%
Cytogenetics / FISH	Normal/+8 (1.6%)	Normal/Normal	Normal/Normal
Indication for HCT	Cytopenias, pRBC transfusion dependent, Trisomy 8 (1.6%)	Cytopenias	Cytopenias, pRBC and platelet transfusion dependent
HCT Characteristics and Outcomes			
Donor / Stem cell source	MRD/marrow	MURD/marrow	MURD/marrow
Follow-up (yr)	Alive, 2.6	Alive, 0.5	Alive, 2.4
Donor chimerism (CD3+/CD33+)[†]	100%/100%	99%/100%	100%/100%
GVHD[§]			
Acute/Chronic (Yes/No)	Yes/No	Yes/No	Yes/No
Day Immune Suppression Stopped	285	Still on	347
Peripheral blood counts[†]			
ANC (cells/μL)	4000	3519	1860
Hematocrit	41%	32%	39%
Platelet Count (cells/μL)	165,000	163,000	216,000
Bone marrow evaluation[†]			
Cellularity	40%-50%	ND	65%
Cytogenetics / FISH	Normal/No evidence of Trisomy 8	ND/ND	Normal/ND
Disease response	Normal blood counts, Transfusion independent, Normal marrow cytogenetics	Resolution of neutropenia and thrombocytopenia, Transfusion independent	Normal blood counts, Transfusion independent

†at last time point studied;

‡mg Iron/g dry weight hepatic tissue, Myocardial: msec;

§Acute grade II–IV GVHD, delayed acute GVHD or NIH chronic GVHD

Abbreviations: HCT, hematopoietic cell transplantation; HCT-CI, hematopoietic cell transplantation comorbidity index; MSD, matched related donor; MURD, matched unrelated donor; ND, not done; pRBC, packed red blood cells; R, recipient; yr, years