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Using Fludarabine to Reduce Exposure to Alkylating Agents in Children with Sickle Cell Disease Receiving Busulfan, Cyclophosphamide, and Antithymocyte Globulin Transplant Conditioning: Results of a Dose De-Escalation Trial

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A B S T R A C T

High-dose busulfan, cyclophosphamide, and antithymocyte globulin (BU-CY-ATG) is the most commonly used conditioning regimen in HLA-matched related hematopoietic cell transplantation for children with sickle cell disease. Disease-free survival with this regimen is now approximately 95%; however, it produces significant morbidity. We hypothesized we could create a less toxic regimen by adding fludarabine (FLU) to BU-CY-ATG and reduce the dosages of busulfan and cyclophosphamide. We conducted a multicenter dose de-escalation trial with the objective of decreasing the doses of busulfan and cyclophosphamide by 50% and 55%, respectively. Using day +28 donor-predominant chimerism as a surrogate endpoint for sustained engraftment, we completed the first 2 of 4 planned levels, enrolling 6 patients at each and reducing the total dose of cyclophosphamide from 200 mg/kg to 90 mg/kg. On the third level, which involved a reduction of i.v. busulfan from 12.8 mg/kg to 9.6 mg/kg, the first 2 patients had host-predominant T cell chimerism, which triggered trial-stopping rules. All 14 patients survive disease-free. No patients suffered severe regimen-related toxicity. Our results suggest BU-FLU-CY-ATG using lower dose CY could be a less toxic yet effective regimen. Further evaluation of this regimen in a full-scale clinical trial is warranted.

INTRODUCTION

Successful trials in North America and Europe established myeloablative busulfan, cyclophosphamide, and antithymocyte globulin (BU-CY-ATG) as the preferred conditioning regimen in HLA-matched related hematopoietic cell transplantation (HCT) for children with sickle cell disease (SCD) [1-3]. Graft rejection, which occurred in about 10% of transplants performed in the 1990s, has become rare, possibly as a result of the widespread adoption of leukocyte-reduced erythrocyte transfusions in the routine management of the complications of SCD. With the marked decrease in rejection, approximately 95% of children transplanted with matched related donors and BU-CY-ATG will be disease-free survivors [1,4].

Although highly effective, BU-CY-ATG causes significant short- and long-term morbidity. Acutely, high-dose BU-CY produces prolonged and severe pancytopenia, resulting in the potential for invasive infections and the need for aggressive erythrocyte and platelet transfusion support [5,6]. BU-CY also causes serious nonhematologic acute toxicities, including mucositis and hepatic sinusoidal obstruction syndrome [5,6]. Although transplant-related mortality is rare in children with SCD, these acute regimen-related complications diminish their health-related quality of life and increase their initial length of stay [7]. Transplant-related hypogonadism is the most

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Table 1
Criteria for Severe SCD

Prior clinical stroke
Asymptomatic but severe cerebrovascular disease as evidenced by 1 of the following:
• Progressive silent cerebral infarction, as demonstrated by serial magnetic resonance imaging scans showing a succession of lesions (≥2 temporally discreet lesions, each measuring ≥3 mm in greatest dimension on most recent scan) or the enlargement of a single lesion, initially measuring ≥3 mm
• Cerebral arteriopathy, as evidenced by abnormal TCD testing (confirmed elevated velocities in any single vessel of TAMMV ≥ 200 cm/s for nonimaging TCD or TAMX > 185 cm/s for imaging TCD)
• Significant vasculopathy on MRA (>50% stenosis of ≥2 arterial segments or complete occlusion of any single arterial segment)
Frequent (≥3 per year for preceding 2 yr) painful vaso-occlusive episodes (defined as episode lasting ≥4 h and requiring hospitalization or outpatient treatment with parenteral opioids)*
Recurrent (≥3 in lifetime) acute chest syndrome events that have necessitated erythrocyte transfusion therapy
Any combination of ≥3 acute chest syndrome episodes and vaso-occlusive pain episodes (defined as above) yearly for 3 yr*

TCD indicates transcranial Doppler ultrasonography; TAMMV, time-averaged mean of the maximum velocity; TAMX, time-averaged mean maximum; MRA, magnetic resonance angiography.

* If patients were on hydroxyurea and its use had been associated with a decrease in the frequency of episodes of acute chest syndrome or painful vaso-occlusion (criteria 3 and 5), the frequency could be gauged from the 3 years before the start of this drug.

common late effect of high-dose BU-CY [8-10]. The risk of infertility often deters many suffering from SCD from pursuing HCT [10,11]. Less toxic conditioning regimens are therefore needed.

We reasoned that we could create a less toxic regimen by adding fludarabine to BU-CY-ATG, using it to reduce the dosages of both busulfan and cyclophosphamide and still achieve engraftment. Fludarabine is a highly immunosuppressive and relatively nontoxic purine analogue [12] that has successfully been incorporated into many reduced-toxicity, reduced-intensity, and minimally toxic conditioning regimens [13-18]. To test our hypothesis, we conducted a multicenter dose de-escalation trial. Our objective was to reduce the doses of busulfan and cyclophosphamide by 50% and 55%, respectively.

METHODS

Study Design and Patients

This study was opened in 2009 as a single-arm, dose de-escalation trial by the Aflac Cancer and Blood Disorders Center of the Children's Healthcare of Atlanta and Emory University. In 2011, it was converted into a multicenter trial and opened at 10 sites. The trial was coordinated by the Aflac Center's clinical research office. The trial was open to children with hemoglobin SS or hemoglobin $S\beta^0$ thalassemia aged 18 years or less with an unaffected HLA-identical sibling donor. Centers were encouraged to use bone marrow grafts; however, cord blood units providing a total nucleated cell (TNC) count $>5.0 \times 10^7$/kg recipient weight could be used in place of marrow. Patients had to have clinically severe SCD, meeting at least 1 of the criteria shown in Table 1.

Protection of Human Subjects

The protocol was approved by the Emory University and all local institutional review boards. Informed consent was obtained from parent/legal guardian or patient, as appropriate, for all patients and assent obtained in accordance with local institutional review board requirements. A rule closing the study to enrollment for 2 deaths was used. This trial was monitored for safety by the Aflac Cancer and Blood Disorders Center Data and Safety Monitoring Board.

Treatment Protocol

Using a regimen comprising 16 i.v. doses of .8 mg/kg busulfan (12.8 mg/kg total), 4 doses of 50 mg/kg cyclophosphamide (200 mg/kg total), and 3 doses of 30 mg/kg horse ATG (90 mg/kg total) as the standard [4], our 4-dose levels comprised 2 reductions in cyclophosphamide followed by 2 reductions in busulfan (Table 2). The standard ATG dose was maintained. Fludarabine was incorporated at a total dose of 105 mg/m^2 for the first 2 dose levels and was then increased to 150 mg/m^2 for the second 2 dose levels. Busulfan was to be administered at .8 mg/kg/dose i.v. every 6 hours for 16 doses (dose level 1 and 2: days −8 to −5), 12 doses (dose level 3: days −7 to −5), or 8 doses (dose level 4: days −6 and −5). Busulfan pharmacokinetic testing was performed with the first dose and dosing adjusted as necessary to achieve a predicted average (over all doses) area under the curve (AUC) of 900 to 1100 mmole · min/L or a concentration steady state of 600 to 750 ng/mL. Cyclophosphamide was to be administered at 45 mg/kg i.v. daily for 3 days (ie, days −4 to −2; dose level 1) or at 30 mg/kg for 3 days (dose levels 2, 3, and 4). Fludarabine was to be administered at 35 mg/m^2 i.v. daily on days −4 to −2 (dose levels 1 and 2) and at 30 mg/m^2 on days −6 to −2 (dose levels 3 and 4). For children weighing more than 125% of their ideal body weight, chemotherapy dosing was based on adjusted ideal body weight. ATG (Atgam, Pfizer, New York, NY) was administered 30 mg/kg i.v. daily on days −4, −3, and −2. Dosing was based on actual body weight.

Two endpoints were considered in the de-escalation schema: day +28 donor-predominant engraftment and severe regimen-related toxicity. Day +28 donor-predominant engraftment was defined as myeloid recovery (absolute neutrophil count ≥500/μL by day +28) with most engrafting cells being donor derived (day +28 chimerism showing >50% of peripheral blood $CD3^+$ and $CD33^+$ cells to be donor derived). This endpoint was derived from experience showing that early donor-predominant engraftment, especially T cell engraftment, is a strong predictor of sustained engraftment in adults with hematologic malignancies who receive minimally toxic conditioning as well as children with malignant or nonmalignant diseases who receive myeloablative or reduced-intensity conditioning [19-21]. Severe regimen-related toxicity was defined as grade 3 or 4 regimen-related organ toxicity occurring by day 42 using the Bearman criteria [22]; in this criteria toxicity is graded from 1 to 4, with grade 4 toxicity being fatal.

Up to 6 patients were enrolled at each dose level. If there were 2 or more cases where donor-predominant engraftment failed to occur, the current dose level and all subsequent dose levels were to be closed to further enrollment. Regimen-related toxicity was only considered in the de-escalation criterion for dose level 1. If there were 3 or more major toxicities at this dose level, then it would be closed to further enrollment, and dose level 2 would be tested. Enrollment was interrupted between patients as needed to assess these endpoints.

For post-transplant immune suppression, cyclosporine and methotrexate were administered to marrow recipients and cyclosporine and mycophenolate mofetil to cord blood recipients. Cyclosporine administration commenced on day −2 using the i.v. formulation and subsequently converted to oral as patients were able to tolerate; doses were adjusted to maintain a level of 200 to 300 ng/mL by the TDx method (or equivalent level for other cyclosporine testing methods). In the absence of graft-versus-host

Table 2
Dose De-Escalation Schema

	Agent					
	Fludarabine (Total Dosage)	Busulfan (Total Dosage)	% Decrease	Cyclophosphamide (Total Dosage)	% Decrease	Horse ATG (Total Dosage)
Standard BU-CY-ATG	—	12.8 mg/kg	—	200 mg/kg	—	90 mg/kg
Level 1	105 mg/m^2	12.8 mg/kg	0	135 mg/kg	32.5	90 mg/kg
Level 2	105 mg/m^2	12.8 mg/kg	0	90 mg/kg	55	90 mg/kg
Level 3	150 mg/m^2	9.6 mg/kg	25	90 mg/kg	55	90 mg/kg
Level 4	150 mg/m^2	6.4 mg/kg	50	90 mg/kg	55	90 mg/kg

disease (GVHD) or tenuous engraftment, a taper was initiated at day 100 and completed by day 180. Methotrexate was administered at a dose of 15 mg/m^2 i.v. (based on actual weight) on day +1 and at 10 mg/m^2 i.v. on days +3 and 6 and 11. Mycophenolate mofetil was administered as 15 mg/kg/dose (maximum dose, 1000 mg) orally (or i.v. if necessary) three times day from day −2 through day +30. Acute and chronic GVHD were characterized according to the U.S. National Institutes of Health consensus criteria [23,24].

All patients were given levetiracetam to prevent busulfan- and cyclosporine-induced seizures and amlodipine to prevent cyclosporine-induced hypertension. Supplemental magnesium beginning on day −2 was recommended to prevent cyclosporine-induced hypomagnesemia. Granulocyte colony-stimulating factor was administered when the absolute neutrophil count failed to reach 500/μL by day +21 or earlier in the management of infection.

Erythrocyte transfusions, simple or exchange, were administered pretransplant as needed to reduce the hemoglobin S percentage to less than 30% pretransplant. Thereafter, erythrocyte transfusions were administered to maintain the hemoglobin level between 9.0 and 11.0 g/dL. Platelets were transfused for platelet counts <50,000/μL. Prevention and treatment of infection was administered according to local practices.

Correlative Studies

A secondary aim of this study was to characterize the cerebrovascular effects of HCT using 2 magnetic resonance imaging biomarkers of ischemic injury, cortical thickness measurement, and diffusion tensor imaging with tract-based spatial statistics and plasma markers of endothelial injury. These assessments are ongoing, and the results will be reported at a later date.

RESULTS

Baseline Characteristics

Fourteen subjects were enrolled between 2009 and 2013. The first 4 subjects were enrolled in Atlanta. With the opening of the trial to other centers in 2011, 6 of the last 10 subjects were enrolled by 4 other centers. The study was closed to enrollment in February 2014 after the primary endpoint was met.

Subjects ranged in age from 4 to 16 years (Table 3). All had hemoglobin SS disease. As in the original North American multicenter trial, cerebrovascular disease was the leading indication for transplant [3]. Unlike that study, however, where overt stroke accounted for almost all such cases, in our study, 4 of 8 participants with cerebrovascular disease qualified for the study by virtue of having abnormal transcranial Doppler velocities. Thirteen participants received bone marrow as their primary graft. Two of these participants also received small cord blood units in addition to the marrow grafts. The median TNC and CD34$^+$ cell marrow doses were 2.8 × 10^8/kg recipient (range, .8 to 5.3) and 6.7 × 10^6/kg recipient (range, 1.0 to 14.2), respectively. Patient 7 (dose level 2) received a cord blood unit, providing 5.1 × 10^7 TNC/kg and 3.9 × 10^5 CD34$^+$ cells/kg as the primary graft. The targeted expected average busulfan AUC of 900 to 1100 mmole · min/L was achieved in all but 1 participant (864 mmole · min/L). The median expected AUC was 968 mmole · min/L (range, 864 to 1093).

Initial Donor Engraftment and Regimen-Related Toxicity

The first 2 patients on dose level 3 failed to meet the threshold of donor-predominate engraftment (>50% donor-derived cells) on day +28, which triggered the stopping criteria for enrollment. Patients 13 and 14 had day +28 donor T cell chimerisms of 38% and 26%, respectively (Table 4). Of note, Patient 13 experienced neutrophil recovery on day +13 and donor myeloid chimerism was 100%. Patient 14 experienced neutrophil recovery on day +22. Myeloid chimerism was unable to be assessed, but whole blood chimerism was 64%. For the 12 participants enrolled before dose level 3, we failed to achieve day +28 donor-predominant engraftment in 2 (1 from level 1 and 1 from level 2). Patient 5's (dose level 1) initial T cell chimerism was 45% donor. Donor myeloid chimerism was 98%, and neutrophil recovery occurred on day +21. Patient 7 (dose level 2), whose primary graft was a cord blood unit, had 26% donor T cell chimerism. Donor myeloid chimerism was 92%, and neutrophil recovery occurred on day +32. None of the participants experienced severe regimen-related toxicity.

Hematologic Outcomes and Long-Term Chimerism

At the time of last follow-up, 8 patients had reached the 24-month mark, and the length of follow-up in the other 6 patients ranged from 9 to 23 months (Table 2). Disease-free survival was 100%. No patient required erythrocyte transfusion support at last follow-up. The median days of neutrophil and platelet recovery (using 50,000/μL as the threshold) were 22 (range, 13 to 32) and 32 (range, 18 to 62). The median number of erythrocyte and platelet transfusions administered post-transplant were 3 (range, 0 to 9) and 12.5 (range, 3 to 28) (Table 5). The median of the most recent hemoglobin level was 12.8 g/dL (range, 9.9 to 15.4). The hemoglobin S percentage

Table 3
Baseline Patient, Disease, and Transplant Characteristics

Patient	Stratum	Recipient Age (yr)/Sex	Type of SCD	Indication for HCT	Donor Age (yr)/Sex	CMV Serostatus (R/D)	Graft	TNC (per kg)	CD34$^+$ (per kg)	Estimated Average AUC (per dose)
1	1	9/M	Hgb SS	Clinical stroke	3/M	+/+	BM	2.3 × 10^8	8.2 × 10^6	989
2	1	10/F	Hgb SS	Clinical stroke	18/F	−/−	BM	3.9 × 10^8	5.0 × 10^6	946
3	1	15/M	Hgb SS	Frequent VOC/ recurrent ACS	10/F	+/+	BM	2.3 × 10^8	3.1 × 10^6	997
4	1	5/F	Hgb SS	Recurrent ACS	4/F	−/−	BM	3.9 × 10^8	1.0 × 10^7	962
5	1	4/F	Hgb SS	Abnormal TCD	1/F	−/−	BM*	2.5 × 10^8	7.1 × 10^6	942
6	1	10/M	Hgb SS	Clinical stroke	1/F	+/−	BM†	.8 × 10^8	2.1 × 10^6	946
7	2	11/M	Hgb SS	Recurrent ACS	8/F	−/+	CB	5.1 × 10^7	3.9 × 10^5	999
8	2	13/M	Hgb SS	Recurrent ACS	19/M	−/+	BM	4.5 × 10^8	6.7 × 10^6	1093
9	2	4/M	Hgb SS	Abnormal TCD	10/M	+/−	BM	5.1 × 10^8	14.2 × 10^6	938
10	2	8/F	Hgb SS	Abnormal TCD	25/F	−/−	BM	1.6 × 10^8	9.0 × 10^6	973
11	2	5/F	Hgb SS	Abnormal TCD	7/F	−/−	BM	2.7 × 10^8	8.6 × 10^6	1011
12	2	10/M	Hgb SS	Recurrent ACS	13/F	−/+	BM	2.8 × 10^8	3.4 × 10^6	906
13	3	16/F	Hgb SS	Frequent VOC	19/F	−/+	BM	4.3 × 10^8	5.2 × 10^6	988
14	3	5/M	Hgb SS	Clinical stroke	11/M	−/−	BM	5.3 × 10^8	7.7 × 10^6	864

CMV indicates cytomegalovirus; R/D, recipient/donor; Hgb, hemoglobin; BM, bone marrow; VOC, vaso-occlusive crisis; ACS, acute chest syndrome; CB, cord blood.

* Patient also received cord blood unit from the same donor (.8 × 10^6 TNC/kg).

† Patient also received cord blood unit from same donor (1.7 × 10^6 TNC/kg).

Table 4
Engraftment, Toxicity, and GVHD

Patient	Stratum	Length of Follow-Up (mo)	Day of Neutrophil Engraftment	Day of Platelet Engraftment	Grade 3/4 RRT	Day +28 Chimerism	Acute GVHD	Chronic GVHD	Neurologic Complications	Status at Last Follow-Up
1	1	24	+19	+43	No	89%/100%	None	None	None	Alive, off immune suppression, PS = 100
2	1	24	+20	+29	No	98%/100%	None	None	None	Alive, off immune suppression, PS = 100
3	1	24	+22	+38	No	77%/100%	None	None	None	Alive, off immune suppression, PS = 100
4	1	24	+22	+33	No	89%/100%	None	None	None	Alive, off immune suppression, PS = 100
5	1	24	+21	+19	No	45/98%	None	None	None	Alive, off immune suppression, PS = 100
6	1	24	+23	+30	No	71/97%	None	None	None	Alive, off immune suppression, PS = 100
7	2	24	+32	+62	No	26/92%	None	None	None	Alive, off immune suppression, PS = 100
8	2	12*	+16	+44	No	71/100%	None	None	None	Alive, off immune suppression, PS = 100
9	2	23	+21	+44	No	94/100	None	None	None	Alive, off immune suppression, PS = 100
10	2	18	+22	+33	No	68/100%	Stage 2 skin, Grade I	Moderate	PRES	Remains on treatment for chronic GVHD, PS = 80
11	2	15	+22	+25	No	77/100$	None	None	None	Alive, off immune suppression, PS = 100
12	2	12	+22	+23	No	71/98%	Stage 2 skin, Grade I	None	None	Alive, off immune suppression, PS = 100
13	3	9	+13	+18	No	38/100	None	Severe	None	Remains on treatment for chronic GVHD, PS = 80
14	3	8	+22	+23	No	28/64%	None	None	None	Alive, tapering immune suppression, PS = 100

RRT indicates regimen-related toxicity; PS, performance status; PRES, posterior reversible encephalopathy syndrome.
* Lost to follow-up.

ranged from 0 to 3% in recipients of transplants from hemoglobin AA donors and from 34% to 42% in recipients of transplants from hemoglobin AS donors. In most patients, $CD3^+$ donor peripheral blood chimerism levels were less than 100% initially and rose overtime. On the other hand, in most patients, $CD33^+$ levels started at 100% and remained there (Figure 1).

Graft-versus-Host Disease

Patients 10 and 12 (dose level 2) developed skin-only grade I acute GVHD that responded to treatment. Patient 10 was placed back on immune suppression, shortly after discontinuation, because she developed chronic GVHD. Her GVHD has progressed and is now severe. Of interest, the chronic GVHD occurred after receiving an influenza vaccine. Patient 13 (dose level 3) developed moderate chronic GVHD without preceding acute GVHD. Patient 14 is nearing the end of his cyclosporine taper with no signs of GVHD. All other patients were successfully weaned off immune suppression.

Neurologic Complications

Patient 10 developed posterior reversible encephalopathy syndrome shortly after initiating treatment (cyclosporine and prednisone) for her chronic GVHD. All clinical and acute

Table 5
Hematologic Outcomes

Patient	Stratum	Most Recent Hemoglobin (g/dL)	Most Recent Hemoglobin S (%)	Number of PRBC Transfusions Post-Transplant	Number of Platelet Transfusions Post-Transplant
1	1	15.1	39.9*	2	14
2	1	13	35.9*	2	11
3	1	15.4	34	2	17
4	1	13.8	0	4	19
5	1	12.3	0	6	7
6	1	12.8	0	2	9
7	2	14.3	40*	7	20
8	2	15.2	41.8	4	24
9	2	12.9	35*	5	28
10	2	10.0	40.3*	2	17
11	2	11.9	39*	2	5
12	2	10.8	0	9	8
13	3	12.8	42*	0	3
14	3	9.9	3	5	3

PRBC indicates packed red blood cell.
* Donor had sickle cell trait.

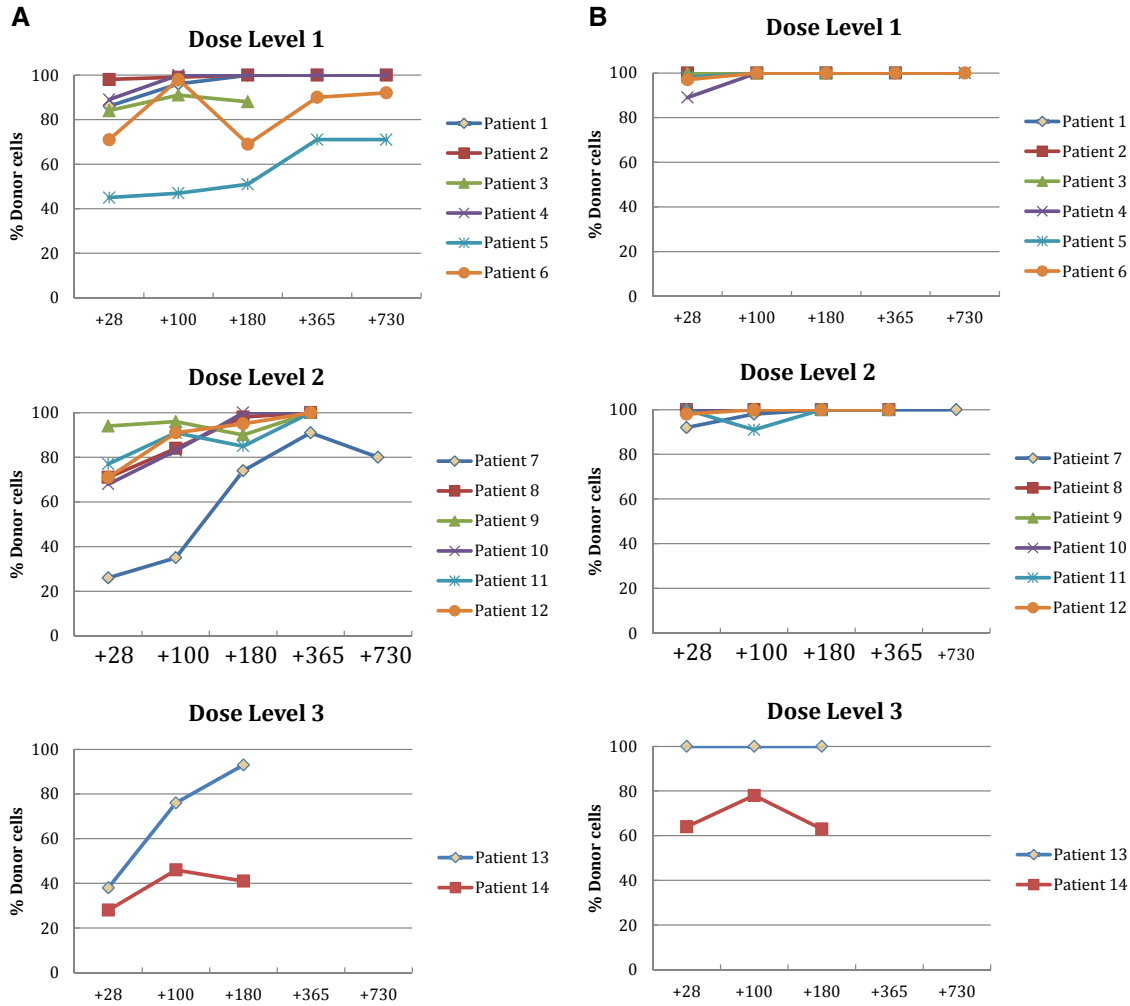

Figure 1. (A) Changes in $CD3^+$ peripheral blood chimerism level over time. (B) Changes in $CD33^+$ peripheral blood chimerism level over time.

radiographic (by magnetic resonance imaging) abnormalities resolved.

DISCUSSION

In this multicenter trial, we demonstrated the feasibility of reducing exposure to cyclophosphamide but not busulfan. As a result, we did not achieve our goal of cutting the exposure to alkylating agents in children receiving BU-CY-ATG for SCD in half. All 6 patients enrolled on dose level 2 achieved sustained donor engraftment, suggesting it may be possible to maintain excellent disease-free survival using 90 mg/kg of cyclophosphamide rather than 200 mg/kg. A full-scale clinical trial is needed to confirm this.

Some may question our decision to use day +28 peripheral blood donor-predominant chimerism (myeloid and T cell) rather than sustained donor engraftment to guide our dose de-escalation. We used early host predominant chimerism, a risk factor for rejection, rather than rejection itself for pragmatic and ethical reasons. Most cases of rejection occur months and some more than half a year post-transplant [3]. Also, graft rejection in patients receiving BU-CY-ATG is now a rare event, affecting no more than 5% of patients [1,4]. To have used rejection as the primary endpoint would have required a sample size and interval of observation impractical for a dose de-escalation trial in this setting. Using a risk factor for rejection rather than rejection also enabled us to minimize the potential harm to the children participating in the trial.

All 3 dose combinations we tested were acutely well tolerated. This is shown by the absence of hepatic sinusoidal syndrome, a relatively common complication in children with SCD receiving standard BU-CY-ATG [4]. With our focus on short-term outcomes and limited sample size, we were unable to assess the effects of the dose reductions on reproductive function; however, given our failure to reduce the dose of the highly gonadotoxic busulfan [25,26], it is unlikely we materially lessened gonadotoxicity. Those of us who care for these children need to make the development of a nongonadotoxic approach a priority.

It is notable that only 1 of 14 participants suffered neurologic toxicity. This is considerably lower than the incidences in previous multicenter studies. Although with our limited sample size we cannot exclude this was due to chance alone, patient or treatment differences could also account for the difference. For seizure prophylaxis we used levetiracetam instead of phenytoin and other older

anticonvulsants used in previous studies [2,3]. It may be that levetiracetam is more effective in this setting. Also, the fact that half of the patients we transplanted for cerebrovascular disease had not previously suffered stroke may have been important. Although the etiology of transplant-related neurologic toxicity remains poorly understood, it is conceivable that patients with less parenchymal damage are less prone to these complications.

We quantified the amount of transfusion support SCD patients receive after transplant for the first time. Our data indicate that the number of transfusions required, both erythrocyte and platelet, varies considerably from patient to patient, and many require substantial platelet transfusion support. Certainly, the use of a higher threshold (50,000/μL), used to prevent intracranial hemorrhage [3,27], accounts in large part for the considerable platelet transfusion requirement. However, other factors may also be important. HLA alloimmunization could influence need for platelet transfusion support, because alloimmunization to class I antigens, which are expressed by platelets, is prevalent in children with SCD [28,29].

In conclusion, the results of our dose de-escalation trial demonstrate that by adding fludarabine to BU-CY-ATG, it is feasible to reduce the dose of cyclophosphamide needed to achieve donor engraftment in children with SCD receiving matched related donor transplants. A full-scale multi-institutional clinical trial is needed to confirm that this 4-drug regimen can maintain disease-free survival at 95%.

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