Umbilical Cord Blood Transplantation for Children with Thalassemia and Sickle Cell Disease

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Abstract

We examined the efficacy of unrelated cord blood (CB) transplantation in children with thalassemia (n = 35) and sickle cell disease (n = 16), using data reported to 3 registries. Donor-recipient pairs were matched at HLA-A and -B (antigen level) and DRB1 (allele level) in 7 or HLA mismatched at 1 (n = 18), 2 (n = 25), or 3 loci (n = 1). Transplant conditioning was myeloablative (n = 39) or reduced intensity (n = 12). Neutrophil recovery with donor chimerism was documented in 24 patients; 11 patients developed grade II-IV acute graft-versus-host disease (aGVHD) and 10 patients, chronic GVHD (cGVHD). Overall survival (OS) and disease-free

survival (DFS) were 62% and 21% for thalassemia and 94% and 50% for sickle cell disease (SCD), respectively. In multivariate analysis, engraftment rate (hazard ratio [HR] 2.2, P=.05) and DFS (HR 0.4, P=.01) were higher with cell dose >5 × 10^7/kg. The 2-year probability of DFS was 45% in patients who received grafts with cell dose >5 × 10^7/kg and 13% with lower cell dose. Primary graft failure was the predominant cause of treatment failure occurring in 20 patients with thalassemia and 7 patients with SCD. Primary graft failure was fatal in 5 patients with thalassemia. These results suggest that only CB units containing an expected infused cell dose >5 × 10^7/kg should be considered for transplantation for hemoglobinopathy.

Keywords

Thalassemia; Sickle cell disease; Cord blood transplantation; Graft failure

INTRODUCTION

Transplantation of hematopoietic stem cells (HSC) from a HLA matched sibling including umbilical cord blood (CB) has been used successfully for thalassemia and sickle cell disease (SCD) [1,2]. Disease-free survival (DFS) rates approach 80% to 90% with transplantation of bone marrow (BM) for sickle cell disease [3,4] and 80% to 95% for beta-thalassemia [5,6]. Despite the availability of over 14 million potential unrelated adult donors registered worldwide, only approximately 17% of African Americans and 20% of Asians who may benefit from unrelated donor transplantation are able to identify a HLA matched unrelated adult donor [7]. As advances in supportive care after transplantation in recent years have led to improvements in survival for patients with hemoglobinopathy [8,9], alternative donor sources such as HLA mismatched family members or unrelated CB units are being explored for patients with hemoglobinopathy. Recent reports suggest DFS rates of approximately 70% for patients with thalassemia who received transplants of allele-level HLA matched unrelated donor BM [10], and similar results are also reported after haploidentical donor transplants [11].

Unrelated cord blood transplantation (CBT) has been explored as an alternative option for these patients without a suitably HLA matched unrelated adult donor. Tolerability of HLA mismatch with relatively low rates of acute and chronic graft-versus-host disease (aGVHD, cGVHD), make CBT a potentially attractive option for those with a hemoglobinopathy. However, CBT may be limited by less than adequate cell dose and higher rates of primary graft failure [12-14]. In a recent report from Taiwan, 27 of 32 patients with thalassemia were disease free at 2 years after CBT with myeloablatve conditioning regimens [15]. In contrast, 4 of 7 patients with SCD after CBT had primary graft failure; importantly, 3 of these 4 patients received reduced-intensity conditioning (RIC) regimens [16]. In the absence of conclusive recommendations on CBT for thalassemia and SCD, we examined outcomes after CBT using data reported to Eurocord, the National Cord Blood Program (NCBP), New York Blood Center, and the Center for International Blood and Marrow Transplant Registry (CIBMTR) to determine the state of the field at the present time.

PATIENTS, MATERIALS, AND METHODS

Patients

Patients with hemoglobinopathy who received transplants of a single unmanipulated CB unit and who were without a history of prior HSC transplantation were eligible; 35 patients had thalassemia, and 16 patients had SCD. Patients reported to 2 or more registries (n = 6) were identified, and each patient included in the current analysis represents a "unique case." CBT were performed at 32 transplant centers between 1996 and 2009. The study was approved by

the institutional review board, Medical College of Wisconsin and the Eurocord-Netcord scientific committee. Myeloablative conditioning regimen was defined as oral (p.o.) busulphan 8 mg/kg or intravenous (i.v.) busulphan 6.4 mg/kg, or melphalan 150 mg/m^2, or total-body irradiation (TBI) (6 Gy) were used.

Endpoints

Neutrophil recovery was defined as achieving absolute neutrophil count (ANC) 0.5×10^9/L for 3 consecutive days with sustained donor engraftment assessed by chimerism assay (95% donor). The timing and method of assay were at the discretion of the transplant center. Primary graft failure was defined as having never achieved ANC 0.5×10^9/L or ANC 0.5×10^9/L without donor engraftment (autologous recovery). Secondary graft failure was defined as having achieved ANC 0.5×10^9/L with subsequent decline to $<0.5 \times 10^9$/L or loss of donor engraftment. Platelet recovery was defined as achieving platelets 20 $\times 10^9$/L unsupported by platelet transfusions for 7 days. The diagnosis and grading of aGVHD and cGVHD was assigned by the transplant center using standard criteria [17,18]. DFS was defined as being alive with donor chimerism. Graft failure, second transplant, and death from any cause were considered events.

Statistical Analysis

Median value and ranges are reported for continuous variables and percentages for categoric variables (Table 1). The probabilities of overall survival (OS) and DFS were calculated using the Kaplan-Meier estimator and the log-rank test for univariate comparisons [19]. The probabilities of neutrophil engraftment, grade acute 2-4 and cGVHD were calculated with the cumulative incidence estimator. Multivariate analyses were performed using Cox proportional hazards regression model for DFS and OS, and Fine and Gray's proportional hazards regression model [20,21].

The variables evaluated included recipient age, donor sex, disease duration before UCBT, ABO compatibility, HLA matching high-resolution DNA typing, number of total nucleated cells (TNCs) at the time of freezing and infusion, conditioning regimen, and year of UCBT. Each potential risk factor was tested independently. All factors that reached a P value = .10 in the univariate analysis were included in the multivariate model. All models were built using a forward stepwise method. Only factors that reached P value .05 were retained in the final model. Patients were censored at death if they underwent a second transplant or for surviving patients, at last follow-up. P values are 2 sided. Statistical analyses were performed with SPSS (Inc., Chicago, IL) and Splus (MathSoft, Inc, Seattle, WA).

RESULTS

Patient, Disease, and Transplant Characteristics

Patient, disease, and transplant characteristics are shown in Table 1. The indications for transplantation were a history of stroke (n = 12) and acute chest syndrome or vaso-occlusive crisis (n = 4) in patients with SCD. As transplantations occurred worldwide and consistent with published reports, the Pesaro risk score was not assigned pretransplant for all patients with thalassemia; only 15 of 35 patients had sufficient data for assignment of the Pesaro classification: class 1 (n = 9), class 2 (n = 2), and class 3 (n = 4). Patients with thalassemia were younger (median, 4 years) compared to those with SCD (median, 6 years). Only 7 donor-recipient pairs were matched at HLA-A and -B (antigen level) and DRB1 (allele level) with the remaining mismatched at 1 (n = 18), 2 (n = 25), or 3 HLA loci (n = 1). Myeloablative conditioning regimens were used in 30 of 35 patients with thalassemia and 9 of 16 with SCD. Busulfan and cyclophosphamide with or without antityhmocyte globulin (ATG) was the most common myeloablative-conditioning regimen. Twelve patients

received RIC and all except 1 received in vivo T cell depletion (ATG or alemtuzumab). All patients received calcinuerin inhibitor containing GVHD prophylaxis, and cyclosporine was the most common agent (65%). The median follow-up of surviving patients with thalassemia and SCD was 21 and 37 months, respectively.

Engraftment and Graft Failure

Twenty-four of 51 patients (n = 15 thalassemia; n = 9 SCD) achieved neutrophil recovery with complete donor chimerism. The median time to neutrophil recovery was 22 days (range: 10-62 days). Two patients had mixed chimerism prior to day 100 but subsequently achieved complete donor chimerism. None of the patients experienced secondary graft failure. In multivariate analysis, engraftment (neutrophil recovery with full donor chimerism) was higher in recipients who received CB units with infused total nucleated cell dose of $>5 \times 10^7$ nucleated cells/kg (hazard ratio [HR] 2.2, 95% confidence interval [CI], 0.96-3.6, P = .05). The day 60 cumulative incidence of engraftment was 63% ± 9% with CB units containing $>5 \times 10^7$ nucleated cells/kg and 32% ± 8% with lower cell dose CB units.

The median time to platelet recovery was 40 days (range: 15-127 days). As with neutrophil recovery, platelet recovery was higher with transplantation of CB units containing total nucleated cells $>5 \times 10^7$/kg (HR 3.4, 95% CI, 1.2-6.2, P = .02). The day 180 cumulative incidence of platelet recovery was 68% ± 9% with CB units containing $>5 \times 10^7$ nucleated cells/kg compared to 25% ± 9% with CB units containing a lower dose.

The characteristics and outcome of the 24 patients who engrafted are shown in Table 2A. Nineteen patients received myeloablative conditioning regimens and 5, RIC regimens. The characteristics of the 27 patients with primary graft failure and their outcome are shown in Table 2B. The cumulative incidence of graft failure was 52% at day 60 and at 1 year. Twenty patients received myeloablative conditioning regimens and 7, RIC regimens. Of these patients with graft failure, 18 had autologous reconstitution, 3 patients received their autologous back-up for prolonged neutropenia and absence of chimerism, 4 patients died without neutrophil recovery, and 2 patients underwent a second allogeneic transplant. Both recipients of second allogeneic HSC transplant are alive with complete donor chimerism with the donor of the second transplant.

Acute GVHD and cGVHD

Eleven patients developed grade 2-4 aGVHD (grade 2 in 8; grade 3 in 2; grade 4 in 1). The cumulative incidence of grade 2-4 aGVHD at day 100 was 23% ± 2%. Ten patients developed cGVHD. Chronic GVHD was extensive in 2 patients and limited in the remaining 8 patients. The cumulative incidence of cGVHD at 2 years was 16% ± 4%.

DFS and OS

Only 16 of 51 patients are alive and disease free (SCD, n = 8; thalassemia, n = 8). DFS was lower in patients with thalassemia (21% ± 7% compared to 50% ± 9% for SCD, P = .05) (Figure 1). In multivariate analysis, DFS was higher with CB units containing total nucleated cell dose $>5 \times 10^7$/kg (HR 0.4, 95% CI, 0.2-0.8, P =.01). The effect of TNC on DFS is independent of disease. The 2-year probability of DFS was 45% ± 9% in recipients of CB units containing a cell dose $>5 \times 10^7$/kg compared to 13% ± 7% for lower cell dose. Although only 16 patients are alive and cured of their disease, 38 of 51 patients are alive largely because of autologous reconstitution after transplantation. All SCD patients with autologous recovery are alive, whereas there were 5 deaths in the thalassemia group. The probabilities of OS for patients with thalassemia and SCD are 62% ± 9% and 94% ± 6%, respectively (Figure 2).

Thirteen patients are dead. Twelve of these patients were transplanted for thalassemia; 7 of these patients had engrafted and died of transplant-related complications. The remaining 5 patients had primary graft failure. Deaths in patients with graft failure may be attributed to patient selection rather than the graft type, a hypothesis that is difficult to test when using data collected by registries. One patient with SCD is dead as a result of severe aGVHD. There were 7 early deaths (100 days after transplantation) because of infection (n = 2), adult respiratory distress syndrome (n = 3), veno-occlusive disease (n = 1), and GVHD (n = 1). Causes of death beyond 100 days were because of opportunistic infection (n = 2), hemorrhage (n = 1), interstitial pneumonitis (n = 1), and multiorgan failure (n = 1). Cause of death was not reported for 1 patient.

DISCUSSION

Allogeneic HSC transplantation offers the only chance of cure for patients with thalassemia major and SCD. However, during the last 3 decades, the medical management of thalassemia or SCD, based primarily on hypertransfusion programs and appropriate chelation treatment or on the use of hydroxyurea, has improved survival of those patients [9,22]. Conventional therapy requires strict compliance of the patients, and therefore the real benefit of an allogeneic transplantation should take these developments into consideration, before indication of such a procedure. In fact, transplantation of BM from a HLA matched sibling remains the standard of care when such a donor is available, with cure rates of 85% for both diseases [4,5,23]. OS after related HLA-matched sibling donor CB transplants are similar to OS after BM transplants in children with malignant and nonmalignant diseases [24], and the same results were observed when analyzing only patients with thalassemia and SCD transplanted with CB or BM from HLA identical sibling donors [25]. Yet another recent approach in the setting of HLA matched sibling transplantation, in order to decrease mortality related to the transplantation procedure, is the use of CD34-selected peripheral blood and a RIC [26]. Of 10 patients treated, 9 patients achieved engraftment with mixed chimerism. Longer follow-up is required to determine whether "mixed chimerism" is stable and capable of curing these patients and eliminating the end-organ effects of the underlying disease. Interestingly, mixed chimerism was not associated with an increased risk of graft failure in a series of 27children with beta-thalassemia who received transplants of CB from a related donor [27].

However, as few patients have a HLA matched sibling donor, most rely on alternative donor transplantation for cure. Transplantation of BM from a HLA matched unrelated adult donor coupled with myeloablative transplant conditioning for thalassemia major approach 80% of survival rate [10,28]. In a recent report, using maternal donors, 14 of 22 patients were reported alive and disease-free with a median follow-up of 40 months [11].

Another alternative donor possibility is the use of cord blood cells; however, there are very few reports on the outcomes after this procedure in patients with hemoglobinopathies. To our knowledge, the current analysis is the largest to date on the impact of UCBT in the treatment of thalassemia and SCD. Engraftment, DFS, and OS for thalassemia are inferior to that reported after unrelated adult donor BM transplantation, and primary graft failure was the most common cause of treatment failure. Graft failure accounted for 25% of deaths in patients with thalassemia. Graft failure was also the most common cause of treatment failure for SCD. However, all patients with SCD who experienced graft failure had autologous reconstitution and are alive. Our findings are consistent with that of others [3,29]. Death from treatment-related complications was common in patients with thalassemia; infection and pulmonary complications were the most common causes of treatment-related mortality. The current analysis is limited in that we could not assign the Pesaro risk score for most patients with thalassemia. It is possible that the 7 patients with thalassemia major who

engrafted and died of a treatment-related complication were "high risk." However, the most common cause of treatment failure, although not necessarily of mortality, was graft failure, which cannot be predicted with the Pesaro risk score. Therefore, the lack of assignment of this risk score does not underscore the validity of our observation for patients with thalassemia after CBT.

The observed high rate of graft failure after unrelated CB transplantation is related to the number of nucleated cells infused. As observed for other nonmalignant diseases, the cell dose of the UCB unit was a major factor associated with engraftment and DFS as well as HLA [30,31]. In the current analysis, engraftment and DFS were higher after transplantation of UCB units containing $>5 \times 10^7$ nucleated cells/kg at the time of infusion, similar to that observed in patients with Fanconi anemia [32].

We know that in the setting of HLA matched sibling and unrelated adult donor BM transplants, increasing pretransplant immune suppression to a myeloablative conditioning regimen is associated with a lower graft failure rate of 5% [4,33]. For UCB, only 1 group has reported 80% DFS at 2 years specifically in recipients of busulfan, cyclophosphamide, and ATG limited to patients with thalassemia [15]. Although most patients in the current analysis received a myeloablative transplant conditioning regimen with ATG or alemtuzumab, DFS was not as good as previously reported by Jaing and colleagues [15]. However, the heterogeneity of transplant conditioning regimens in the current analysis precludes definitive recommendations other than increasing pretransplant immune suppression to facilitate engraftment. New conditioning regimens more likely to effect sustained engraftment are needed for this patient population.

Indeed, graft failure after umbilical CBT is multi-factorial including known factors such as disease, HLA-disparity, cell dose, conditioning regimen, as well as several unknown and unmeasured factors that may include matching at HLA-C locus and presence of HLA antibodies [34]. Recently, the Japanese group [35] reported on the impact of anti-HLA antibodies on the engraftment rate. In this series among 386 UCBT, 89 tested positive for anti-HLA antibodies, and 20 cases had specificity against the cord blood HLA. Patients with antibodies against the cord blood graft had significant higher graft failure rate. We do not have donor-recipient samples, which prevent us from examining for the impact of HLA antibodies on graft failure in our population. Additionally, all patients in the current analysis were transfused prior to transplantation, and we cannot exclude the possibility of alloimmunization and its effect on engraftment. Taken together, the transplantation strategies using unrelated CB as the stem cell source is suboptimal for patients with hemoglobinopathy. Graft failure remains a major limitation to success, and the continuing use of CB for this disease must be discouraged outside of well-designed novel clinical trials. One potential strategy may be the use of 2 CB units in order to achieve the desired cell dose as has been done in patients with malignancy [36]. However, early reports suggest that the double CB transplant approach may be associated with a higher rate of aGVHD, which may add to the burden of morbidity and mortality for such a patient population [37]. Indeed, no data have yet been reported on double CB transplant for hemoglobinopathies. An alternative is HSC transplantation [11]. Results are encouraging, and a larger series is needed to confirm the observed success after this strategy. Other strategies such as preimplantation genetics and embryo selection [38] or gene therapy to correct the beta-globin synthesis [39] for those with access to this technology are currently under investigation and may optimize outcomes.

Acknowledgments

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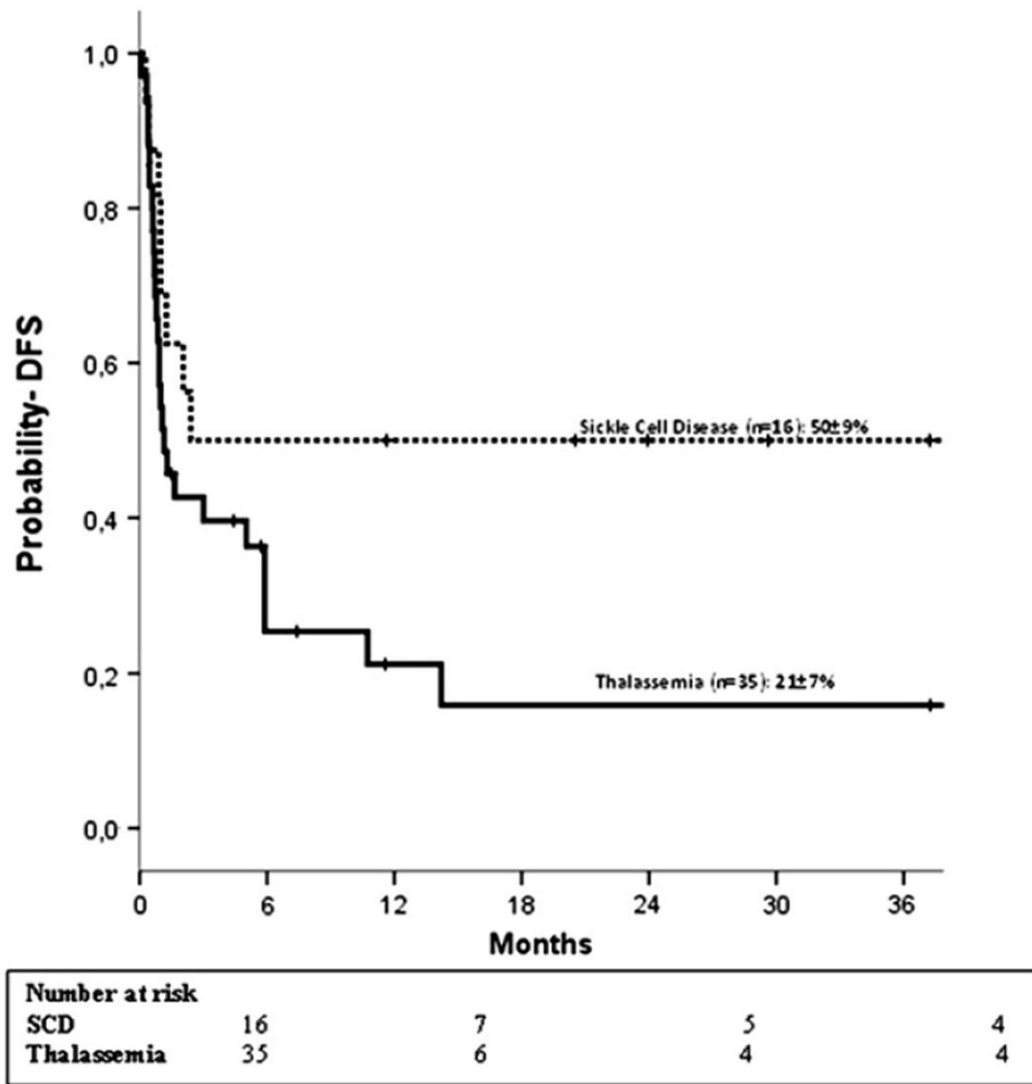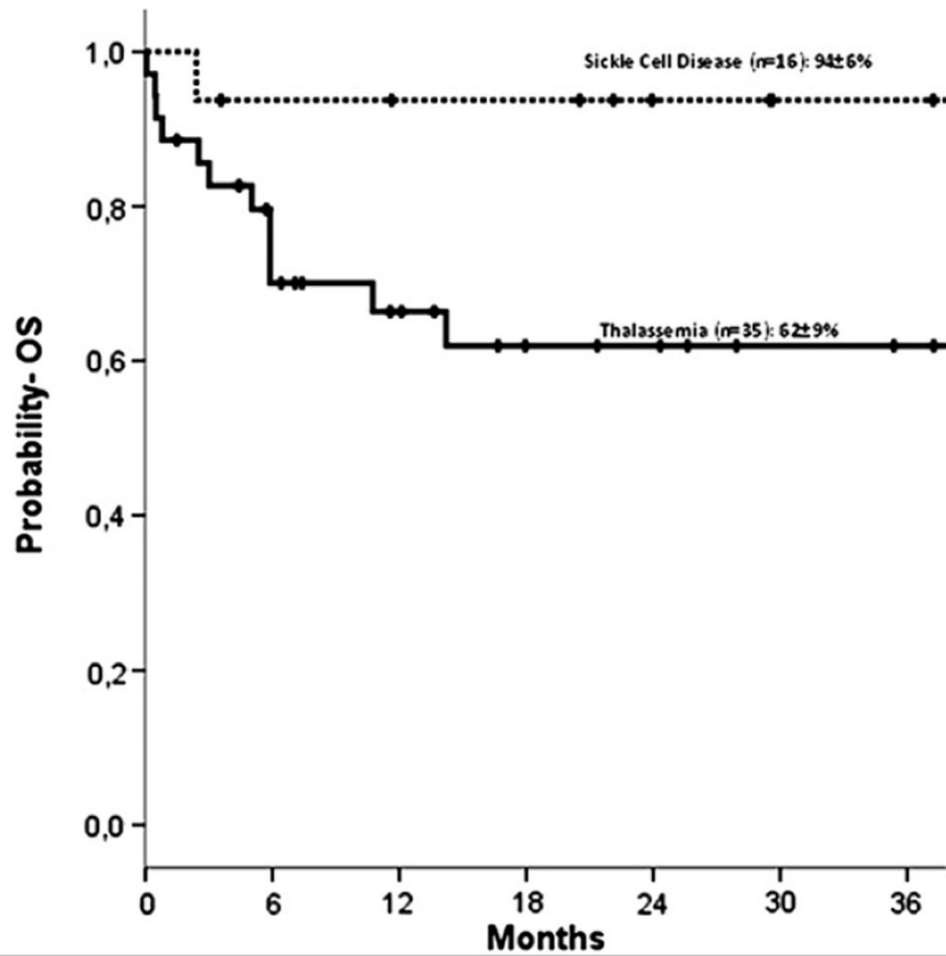
Figure 1.
Estimated 2-year DFS according to diagnosis (••• sickle cell disease; — thalassemia).

Figure 2.
Estimated 2-year OS according to diagnosis (••• sickle cell disease; — thalassemia.

Table 1

Patient, Disease, and Transplant Characteristics

	Thalassemia	Sickle Cell Disease
Number evaluation	35	16
Sex male, %	58%	75%
Interval from diagnosis to transplant, months	29 (3-169)	76 (7-191)
Conditioning regimen		
Myeloablative regimens, n	30	9
Busulfan + cyclophosphamide (Cy) + ATG	27	6
Busulfan + fludarabine + Cy	2	—
Busulfan + fludarabine	—	—
Busulfan + Cy +Thiotepa + ATG	1	—
Busulfan + fludarabine + alemtuzumab	—	1
Busulfan + melphalan	—	1
Busulfan + melphalan + ATG	—	1
Reduced-intensity regimens, n	5	7
Busulfan + fludarabine + TLI + ATG/alemtuzumab	1	2
Melphalan + fludarabine + ATG/alemtuzumab	1	2
Cy + fludarabine ± TLI + ATG/alemtuzumab	2	3
Fludarabine ± TB 200 Gy	1	—
Use of ATG/Campath before day 0, %	86%	94%
GVHD prophylaxis		
Cyclosporine based,n, %	27 (80%)	9 (54%)
Tacrolimus based, n, %	8 (20%)	7 (46%)
Donor-recipient HLA match, n		
6/6 matched	5	2
5/6 matched	14	4
4/6 matched	15	10
3/6 matched	1	—
Total nucleated cell dose, at collection/kg (10^7)	6 (2-32)	6 (2-12)
Total nucleated cell dose, infused/kg (10^7)	5 (2.4-23)	4.9 (1.1-9)
Median follow-up of surviving patients	21 (3-138)	37 (3-80)

GVHD indicates graft-versus-host disease; ATG, antithymocyte globulin; YLI, total lymphoid irradiation.

Table 2

A. Characteristics of Patients Who Engrafted with Donor Chimerism

Patient	Age, Years	Diagnosis	Median Disease Duration, Months	Conditioning Regimen	GVHD Prophylaxis	Donor-Recipient HLA Match	TNC Infused, (10^7/kg)	Follow-Up, Months	Status	Cause of Death
1	8	Sickle cell disease	20	Cy+Bu+ATG	FK506	5/6 matched	—	23.93	alive	
2	9	Sickle cell disease	106	Cy+Bu+ATG	CsA+Pred	5/6 matched	6.9	63.50	alive	
3	6	Sickle cell disease	76	Bu+Fluda+Alemtuzumab *	FK506+MMF	4/6 matched	3.5	37.22	alive	
4	8	Sickle cell disease	97	Fluda+Melph+Alemtuzumab *	CsA+MTX+Pred	4/6 matched	—	11.64	alive	
5	5	Sickle cell disease		Cy+Bu+Fluda	CsA+Pred	5/6 matched	11	2.41	dead	GVHD
6	3	Sickle cell disease	39	Cy+Bu+ATG	FK506+Pred	4/6 matched	9.3	80.50	alive	
7	3	Sickle cell disease	37	Cy+Bu+ATG	CsA+Pred	6/6 matched	5.1	20.53	alive	
8	12	Sickle cell disease	151	Cy+Bu+ATG	Other	4/6 matched	1.7	79.44	alive	
9	4	Sickle cell disease	54	Cy+Fluda+Alemtuzumab *	FK506+MMF	4/6 matched	9.1	29.62	alive	
10	4	Thalassemia	26	Cy+Bu+ATG	CsA+Pred	4/6 matched	7.1	10.74	dead	Unknown
11	1	Thalassemia	15	Cy+Bu+Fluda	CsA+MMF	5/6 matched	15.2	11.57	alive	
12	0.3	Thalassemia	4	Cy+Fluda *	CsA+Pred	6/6 matched	3.9	3.01	dead	Veno-occlusive disease
13	15	Thalassemia	—	Cy+Bu+ATG	CsA	4/6 matched	3.3	5.88	dead	MOF
14	2	Thalassemia	20	Cy+Bu+ATG	CsA+Pred	5/6 matched	4.9	44.36	alive	
15	8	Thalassemia	101	Cy+Bu+ATG	CsA+Pred	4/6 matched	4.3	14.21	dead	Infection
16	1	Thalassemia	—	Fluda+Melph+ATG *	Other	6/6 matched	7.6	7.40	alive	
17	5	Thalassemia	3	Cy+Bu+ATG	FK506	5/6 matched	8.7	4.43	alive	
18	4	Thalassemia	64	Cy+Bu+ATG	Other	5/6 matched	7.4	5.88	dead	Hemorrhage
19	2	Thalassemia	26	Cy+Bu+ATG	CsA+Pred	4/6 matched	1.4	5.88	dead	Interstitial pneumonitis
20	3	Thalassemia	43	Cy+Bu+ATG	FK506+MMF	6/6 matched	11	5.72	alive	
21	0.2	Thalassemia	7	Cy+Bu+ATG	CsA+Pred	4/6 matched	1.9	91.07	alive	
22	1	Thalassemia	—	Cy+Bu+ATG	CsA+MTX	5/6 matched	9.6	1.49	alive	
23	5	Thalassemia	29	Cy+Bu+ATG	CsA+MMF+ Pred	5/6 matched	7.1	5.02	dead	Infection
24	2	Thalassemia	19	Cy+Bu+ATG	FK506	5/6 matched	5.1	37.26	alive	

B. Characteristics of Patients with Primary Graft Failure

Patient	Age, Years	Diagnosis	Median Disease Duration, Months	Conditioning Regimen	GVHD Prophylaxis	Donor-Recipient HLA Match	TNC Infused, (10^7/kg)	Follow-Up, Months	Status	Cause of Death
1	6	Sickle cell disease	77	Cy+Bu+ATG	FK506	4/6 matched	5.6	72.36	alive	
2	5	Sickle cell disease	59	Bu+Fluda+TLI+ATG[‡]	CsA+MMF	6/6 matched	5.8	29.52	alive	
3	9	Sickle cell disease	107	Bu+Melph+ATG	CsA	5/6 matched	3	41.22	alive	
4	1	Sickle cell disease	7	Cy+Fluda[‡]	FK506+MMF	4/6 matched	4.7	22.12	alive	
5	5	Sickle cell disease	62	Cy+Bu+ATG	FK506	4/6 matched	4.2	3.57	alive	
6	8	Sickle cell disease	100	Cy+Fluda+TLI+ATG[‡]	CsA+Pred	4/6 matched	4	45.29	alive	
7	17	Sickle cell disease	191	Fluda+Melph+ATG[‡]	CsA+Pred	4/6 matched	1.4	56.23	alive	
8[*]	0/5	Thalassemia	6	Bu+Fluda	FK506+MMF	5/6 matched	9.52	75.57	alive	
9	15	Thalassemia	73	Cy+Bu	Other	3/6 matched	3.7	24.33	alive	
10	10	Thalassemia	96	Cy+Bu	CsA+MTX	5/6 matched	3.2	16.66	alive	
11	6	Thalassemia	69	Cy+Bu+ATG	CsA+MMF+Pred	5/6 matched	3.3	7.07	alive	
12	2	Thalassemia	22	Cy+Bu+ATG	CsA	5/6 matched	15	21.36	alive	
13[†]	11	Thalassemia	124	Cy+Bu+ATG	CsA+Pred	5/6 matched	2.6	45.75	alive	
14	6	Thalassemia	57	Cy+Bu+ATG	Other	6/6 matched	5.8	17.95	alive	
15[*]	1	Thalassemia	9	Bu+Fluda+TLI+ATG§	CsA+MMF	4/6 matched	5.3	43.54	alive	
16	4	Thalassemia	46	Fluda+Melph+ATGh[‡]	FK506	6/6 matched	3.7	35.37	alive	
17	7	Thalassemia	33	Cy+Bu+ATG	CsA+Pred	4/6 matched	4.5	0.07	dead	ARDS
18	6	Thalassemia	28	Cy+Bu+ATG	CsA+MMF	5/6 matched	9.2	0.46	dead	ARDS
19	1	Thalassemia	5	Cy+Bu+ATG	CsA+Pred	4/6 matched	23.3	0.5	dead	ARDS
20	2	Thalassemia	23	Cy+Bu+ATG	CsA+MMF	4/6 matched	6.5	12.1	alive	
21	2	Thalassemia	30	Cy+Bu+ATG	Other	4/6 matched	4.9	6.41	alive	
22	14	Thalassemia	169	Fludarabine[‡]	CsA+MMF	4/6 matched	3.7	2.51	dead	Infection
23	8	Thalassemia	97	Cy+Bu+ATG	CsA+Pred	4/6 matched	4.8	27.93	alive	
24[†]	2	Thalassemia	25	Cy+Bu+ATG	CsA+Pred	5/6 matched	4.6	137.88	alive	
25	9	Thalassemia	98	Cy+Bu+ATG	Other	4/6 matched	2.4	0.79	dead	Infection
26	6	Thalassemia	74	Cy+Bu+ATG	CsA	4/6 matched	3.7	25.62	alive	
27[†]	1	Thalassemia	4	Cy+Bu+Thio+ATG	CsA	4/6 matched	12	13.65	alive	

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ATG indicates serum antilymphocyt; Bu, busulfan; CsA, cyclosporine A; Cy cyclophosfamide; Fluda, fludarabine; Melph, melphalan; MMF, mycophenolate mofetil; MTX, methotrexate; MOF, multiorgan failure; Pred, prednisone.

*
Reduced-intensity conditioning.

aGVHD indicates acute graft-versus-host disease; ARDS, acute respiratory distress syndrome; ATG, serum antilymphocyt; Bu, busulfan; CsA, cyclosporine A; Cy, cyclophosfamide; Fluda, fludarabine; Melph, melphalan; MMF, mycophenolate mofetil; MTX, methotrexate; Thio, Thiotepa; Pred, prednisone; TNC, total nuclease cell; TLI, total lymphoid irradiation.

*
Second hematopoietic stem cell transplantation (HSCT).

†
Autologous backup.

‡
Reduced-intensity conditioning (RIC).