Biology of Blood and Marrow Transplantation 11:600-608 (2005)

1083-8791/05/1108-0005$30.00/0
doi:10.1016/j.bbmt.2005.05.005

Bone Marrow Transplantation for Diamond-Blackfan Anemia

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Received November 18, 2004; accepted May 10, 2005

ABSTRACT

Patients with Diamond-Blackfan anemia (DBA) who are unresponsive to or intolerant of corticosteroids, experience treatment failure with other treatments, develop additional cytopenias or clonal disease, or opt for curative therapy are often treated with allogeneic bone marrow transplantation. We studied the transplantation outcomes of 61 DBA patients whose data were reported to the International Bone Marrow Transplant Registry between 1984 and 2000. The median age was 7 years (range, 1-32 years). Among 55 patients with available transfusion information, 35 (64%) had received ≥20 units of blood before transplantation. Most patients (67%) received their bone marrow grafts from an HLA-matched related donor. The median time to neutrophil recovery was 17 days (range, 10-119 days) and to platelet recovery was 23 days (range, 9-119 days). Five patients did not achieve neutrophil engraftment. The 100-day mortality was 18% (95% confidence interval, 10%-29%). Grade II to IV acute graft-versus-host disease occurred in 28% (range, 17%-39%) and chronic graft-versus-host disease in 26% (range, 15%-39%). The 3-year probability of overall survival was 64% (range, 50%-74%). In univariate analysis, a Karnofsky score ≥90 and transplantation from an HLA-identical sibling donor were associated with better survival. These data suggest that allogeneic bone marrow transplantation is effective for the treatment of DBA. Transplantation before deterioration of the performance status and from an HLA-identical sibling donor may improve survival.

KEY WORDS

Bone marrow transplantation • Diamond-Blackfan anemia • Congenital anemia

INTRODUCTION

Diamond-Blackfan anemia (DBA) is a rare, congenital, pure red cell aplasia caused by an intrinsic erythroid regenerative defect [1,2]. The molecular event responsible for this single lineage defect is not completely known in all patients. Approximately 25% of cases are associated with a mutation in ribosomal protein RPS19 that results in RPS19 protein haploinsufficiency [3,4]. Because there are no clear correlations between the mutated RPS19 and the clinical phenotype, even within a multiplex family, it is likely that additional molecular events collaborate for the development of this disease [5,6].

DBA is predominantly a disease of childhood. Clinical features of DBA include normocytic or macrocytic anemia, reticulocytopenia, and bone marrow erythrocytopenia. The natural history of DBA is variable; although approximately 20% of patients may become transfusion or corticosteroid independent, most will eventually require long-term treatment [7]. Approximately 80% of patients have an initial re-

sponse to corticosteroids [8]. Other agents—such as androgens, cyclosporine, intravenous gamma globulin, metoclopramide, or erythropoietin—have been used with limited success in steroid-refractory patients [9-14]. Patients unresponsive to or unable to tolerate medical therapies require chronic red cell transfusions and are at risk for iron overload, with its consequent complications.

Allogeneic bone marrow transplantation (BMT) is a potentially curative treatment option for DBA. Since the first report in 1976 of correction of hematopoiesis after BMT, several authors have reported successful transplantation for selected patients with DBA [15-22]. However, these reports are limited by small numbers of patients. The largest report to date, from the Diamond-Blackfan Anemia Registry, had 20 patients. We analyzed the data reported to the International Bone Marrow Transplant Registry (IBMTR) to determine outcomes after HLA-matched related (n = 41) and alternative donor (n = 20) BMT in 61 patients with DBA. This is the largest body of experience on allogeneic transplantation outcomes in this disease.

PATIENTS AND METHODS

Data Sources

The IBMTR is a voluntary working group of more than 400 transplant centers worldwide that contribute detailed data on consecutive allogeneic hematopoietic stem cell transplantations to a statistical center at the Health Policy Institute of the Medical College of Wisconsin in Milwaukee. On the basis of data collected in the Centers for Disease Control Hospital Surveys and US Government Accounting Office and worldwide surveys of transplantation activity, approximately 40% of allogeneic transplantations worldwide are registered with the IBMTR. Participating centers are required to report all transplantations consecutively; compliance is monitored by on-site audits. Patients are followed up longitudinally, with yearly follow-up.

The IBMTR collects data at 2 levels: registration and research. Registration data include disease type, age, sex, pretransplantation disease stage and chemotherapy responsiveness, date of diagnosis, graft type (bone marrow, blood-derived stem cells, or cord blood), pretransplantation conditioning regimen, posttransplantation disease progression and survival, development of a new malignancy, and cause of death. Participating transplant centers register consecutive transplantations. Research data are collected on a subset of registered patients selected by using a weighted randomization scheme and include detailed disease and pretransplantation and posttransplantation clinical information. Computerized checks for errors, physician reviews of submitted data, and on-site audits of participating centers ensure the quality of data. Observational studies conducted by the IBMTR are performed with a waiver of informed consent and in compliance with Health Insurance Portability and Accountability Act regulations as determined by the Institutional Review Board and the Privacy Officer of the Medical College of Wisconsin.

Patients

Ninety-three patients were registered as having received a transplant between 1984 and 2000. Of these, comprehensive patient, disease, and transplantation characteristics were available on 61 (66%) of 93 patients. The diagnosis of DBA was reported by the transplant center, and the decision to proceed to transplantation was at the discretion of the transplant center. Patient, disease, and transplant characteristics and overall survival of those with or without comprehensive data were similar (overall survival at 3 years, 63% [range, 53%-73%] versus 64% [range, 50%-74%]; $P = .93$). Eligible cases came from 37 reporting teams from 17 countries. The median follow-up of survivors was 126 months (range, 12-164 months).

End Points

Primary end points were neutrophil and platelet recovery, 100-day mortality, acute and chronic graft-versus-host disease (GVHD), and overall survival. Hematopoietic recovery was defined as achieving an absolute neutrophil count $\geq 0.5 \times 10^9$/L for 3 consecutive days and platelets $\geq 20 \times 10^9$/L (untransfused). Acute and chronic GVHD were defined as grade II to IV acute GVHD and any chronic GVHD (limited or extensive), respectively [23,24]. For analyses of overall survival, failure was death from any cause; surviving patients were censored at the date of last contact.

Statistical Analysis

The probabilities of neutrophil and platelet recovery and acute and chronic GVHD were calculated by using cumulative incidence rates to accommodate competing risks; probabilities of day 100 mortality and overall survival were calculated by using the Kaplan-Meier estimator [25,26]. Estimates of standard error for the survival function were calculated by Greenwood's formula, and 95% confidence intervals (CI) were calculated by using log-transformed intervals [27]. Assessment of potential prognostic factors for survival was limited to univariate analysis because of the small sample size. Table 1 shows variables considered in univariate analysis. Variables not listed in the final analysis did not meet the 5% level of significance. P values for differences in outcomes between groups were calculated by using the point-wise estimator. All P values are 2 sided. All computations were performed

Table 1. *Variables Considered in the Univariate Analysis*

Patient-related variables
Age at transplantation: ≤10 vs. >10 y
Sex: female vs. male
Karnofsky performance score at transplantation: <90 vs. ≥90
Disease-related variables
Number of transfusions before transplantation: ≤20 vs. >20
TBI for conditioning regimen: yes vs. no
Nucleated cell dose: ≤4 × 10^8/kg vs. >4 × 10^8/kg
Time from diagnosis to transplantation: ≤60 vs. >60 mo
Treatment-related variables
Donor-recipient sex match: F-M vs. others
Donor-recipient CMV status: donor-recipient negative vs. others
Type of donor: HLA-identical sibling vs. others
Year of transplantation: <1990 vs. ≥1990
Growth factors after transplantation: yes vs. no

by using the statistical package SAS version 8.0 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

Patient-, disease-, and treatment-related characteristics are summarized in Table 2. The median age at transplantation was 7 years (range, 1-32 years). Twenty-five (41%) of 61 patients were male. Most patients (68%) had a pretransplantation Karnofsky performance score of 90 or 100. Most (93%) had received steroids, and 48% had received additional therapies before transplantation. Among the 55 patients with available information on transfusions, 28 patients (51%) received 1 to 50 transfusions, and 27 (49%) received >50 transfusions. All patients received bone marrow grafts.

Of the 61 patients in this study, 46 (75%) underwent transplantation after 1989. The registry data on transplantation outcomes in 10 patients with DBA (1984 to 1990) have previously been reported [17]. Two patients included in this article who underwent transplantation in 1990 were also included in the previous article. Forty-one patients (67%) received transplants from an HLA-identical sibling donor, 8 (13%) from a nonsibling family donor, and 12 (20%) from a matched unrelated donor. Patients underwent transplantation a median of 62 months after diagnosis (range, 5-286 months). All patients except 1 in this series received conventional, cyclophosphamide-based conditioning regimens. Only 18% of patients received total body irradiation. The median number of mononuclear cells transplanted per kilogram recipient weight was 4 × 10^8/kg (range, 1-12 × 10^8/kg). Cyclosporin A and methotrexate were the most frequently used agents for GVHD prophylaxis. Approximately one quarter of patients started hematopoietic growth factors within 7 days after transplantation. Patients who received an alternative donor transplant were more likely to be older (9 versus 5 years; P = .03), to have had a longer median time from diagnosis to transplantation (110 versus 58 months; P = .02), and to have received total body irradiation as part of the conditioning regimen (45% versus 5%; P < .001).

Outcomes

Hematopoietic recovery. Fifty-four of 59 evaluable patients achieved neutrophil recovery. Among those who achieved neutrophil recovery, the median time to recovery was 17 days (range, 10-119 days). The probability of neutrophil recovery at day 100 was 90% (95% CI, 81%-95%) after transplantation from any donor (Table 3). Among patients who were heavily transfused (>50 transfusions) before BMT, the probability of neutrophil recovery at day 28 was lower (67% [95% CI, 46%-85%] versus 89% [95% CI, 81%-95%]; P = .04). However, by days 60 and 100, there were no significant differences between groups. The characteristics of the 5 patients who did not achieve neutrophil recovery did not differ from those of patients who achieved recovery (ie, age, number of transfusions before BMT, interval from diagnosis to BMT, donor type, donor-recipient ABO compatibility, and cell dose). The median time for platelet recovery was 23 days (range, 9-119 days). Fifty-one percent of patients achieved platelet recovery at 28 days after transplantation, and 75% achieved platelet recovery at 100 days. The tempo of platelet recovery among heavily transfused patients was slower. Even though recovery rates were not statistically different at 28 and 100 days after transplantation, at 60 days, the proportion of patients with platelet recovery was significantly higher in patients who had received ≤50 red blood cell transfusions compared with those who received >50 red blood cell transfusions (85% [95% CI, 71%-95%] versus 63% [95% CI, 44%-79%]; P = .04).

Graft-versus-host disease. The cumulative incidence of grade II to IV acute GVHD was 28% (95% CI, 17%-39%) (Table 3). There were no differences in the incidence of acute GVHD by donor type. The cumulative incidence of chronic GVHD at 3 years was lower among recipients of HLA-identical sibling donor grafts compared with recipients of other donor grafts (18% [95% CI, 7%-32%] vs 51% [95% CI, 26%-77%]; P = .03). The number of patients who received unrelated or mismatched related grafts was too small to meaningfully evaluate whether the risk of acute or chronic GVHD was higher in these patients compared with patients who received matched related donor transplants. Chronic GVHD occurred in 19% (95% CI, 9%-28%), 26% (95% CI, 15%-39%), and 29% (95% CI, 17%-43%) of patients at 1, 3, and 5 years, respectively (Table 3).

Survival and disease response. The probabilities of

Table 2. *Characteristics of Patients Who Underwent Allogeneic Bone Marrow Transplantation for Diamond-Blackfan Anemia until 2000*

Patient Characteristics	No. Evaluable	Data
No. patients		**61**
Age, y, median (range)	**61**	**7 (1–32)**
Age >10 y	**61**	**20 (33)**
Male sex	**61**	**25 (41)**
Karnofsky score ≥90	**60**	**41 (68)**
Pretransplantation therapy	**60**	
None		**4 (7)**
Steroids alone		**27 (45)**
Steroids + other*		**29 (48)**
No. of transfusions before transplantation	**55**	
1–20		**20 (36)**
21–50		**8 (15)**
>50		**27 (49)**
Conditioning regimen	**61**	
BuCy ± other		**44 (72)**
CyRad ± other		**13 (21)**
Other†		**4 (7)**
Nucleated cell dose, $\times 10^8$/kg, median (range)	**56**	**4 (1–12)**
Nucleated cell dose >4 × 10^8/kg	**56**	**25 (45)**
Donor-recipient sex match‡	**59**	
M-M		**16 (27)**
M-F		**13 (22)**
F-M		**9 (15)**
F-F		**21 (36)**
Donor-recipient CMV status	**50**	
+/+		**19 (38)**
+/−		**6 (12)**
−/+		**5 (10)**
−/−		**20 (40)**
Donor-recipient ABO compatibility§	**53**	
Match		**27 (51)**
Minor mismatch		**10 (19)**
Major mismatch		**10 (19)**
Bidirectional mismatch		**6 (11)**
Donor type	**61**	
HLA-identical sibling		**41 (67)**
Other relative‖		**8 (13)**
Unrelated¶		**12 (20)**
Time from diagnosis to transplantation, mo, median (range)	**61**	**62 (5–286)**
Time from diagnosis to transplantation >60 mo	**61**	**33 (54)**
Year of transplantation	**61**	
≤1989		**15 (25)**
1990–1995		**24 (39)**
1996–2000		**22 (36)**
GVHD prophylaxis#	**61**	
None		**2 (3)**
MTX ± other		**4 (7)**
CsA ± other		**12 (20)**
MTX + CsA ± other		**38 (62)**
T-cell depletion ± other		**5 (8)**
G-CSF or GM-CSF given within 7 days after transplantation	**61**	**14 (23)**

Bu indicates busulfan; CsA, cyclosporine; Cy, cyclophosphamide; GVHD, graft-versus-host disease; MTX, methotrexate; CMV, cytomegalovirus; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; Rad, combination of total body, total lymph node, and total abdominal irradiation.

Data are n (%) unless otherwise marked.

*Other pretransplantation therapies included cyclosporine, other immunosuppressive agents given alone, cytokines, cyclosporine + cytokines, cyclosporine + cytokines + intravenous immunoglobulin, antithymocyte globulin (ATG), ATG + cytokines, ATG + other immunosupressive agents, ATG + cyclosporine, ATG + cyclosporine + cytokines, androgens, androgens + cytokines, and other combinations.

†Other conditioning regimens were cyclophosphamide + other (n = 3) and total body irradiation (TBI) + fludarabine (n = 1). Eleven (18%) of 61 received TBI as part of the conditioning regimen.

‡Two recipient-donor sex matches are unknown; however, they were a complete HLA match.

§ABO compatibility: ABO matched = donor and recipient are the same ABO blood group; minor mismatch = donor with blood group O into recipient with blood group A, B, or AB and donor with blood group A or B into recipient with blood group AB; major mismatch = donor with blood group A, B, or AB into recipient with blood group O and donor with blood group AB into recipient with blood group A or B; bidirectional = donor with blood group A into recipient with blood group B and donor with blood group B into recipient with blood group A.

‖Three in the "other relative" donor category were parents.

¶Unrelated donors were matched by using a serologic method for -A and -B and molecular typing for -DR.

#Other GVHD prophylaxes were corticosteroids, ATG, anti–T-lymphocyte monoclonal antibody, and cyclosporine.

Table 3. *Transplantation Outcomes among Patients Who Underwent Allogeneic Transplantation for Diamond-Blackfan Anemia until 2000*

Outcome	No. Evaluable	Data*
VOD of the liver, n (%)	56	8 (14)
100-d mortality	61	18 (10–29)
Time to ANC >0.5 × 10^9/L, median (range)†	54	17 (10–119)
ANC >0.5 × 10^9/L	59	
28 d		78 (66–86)
100 d		90 (80–95)
Time to platelets >20 × 10^9/L, median (range)	55	23 (9–119)
Platelets >20 × 10^9/L	55	
28 d		51 (38–63)
100 d		75 (63–85)
Acute GVHD at 100 d, grades II to IV‡	58	28 (17–39)
Chronic GVHD§	49	
1 y		19 (9–28)
3 y		26 (15–39)
Survival	61	
1 y		67 (54–77)
3 y		64 (50–74)

GVHD indicates graft-versus-host disease; VOD, veno-occlusive disease; ANC, absolute neutrophil count.

Data are probability (95% confidence interval) % unless otherwise marked.

*The 100-day mortality was calculated with the χ^2 test. Probabilities of acute GVHD, chronic GVHD, and engraftment were calculated by using the cumulative incidence estimate. Survival was calculated by using the Kaplan-Meier product-limit estimate.

†Among patients who achieved neutrophil recovery.

‡Patients are at risk for this event at 21 days after transplantation with evidence of engraftment (2 patients were excluded).

§Patients are at risk for this event at 90 days after transplantation (12 patients were excluded).

overall survival at 1 and 3 years after transplantation were 67% (95% CI, 54%-77%) and 63% (95% CI, 50%-74%), respectively (Table 3). A Karnofsky score ≥90 was associated with improved 100-day (93% versus 63%; $P < .01$) and 3-year (75% versus 42%; $P = .01$) survival (Table 4 and Figure 1). Transplantation from an HLA-identical sibling donor (versus alternative donors) was also associated with improved overall survival at 1 and 3 years (78% versus 45% [$P = .01$] and 76% versus 39% [$P = .01$], respectively; Figure 2). The 1- and 3-year probability of overall survival of patients with a good performance status who received allografts from HLA-identical sibling donors (n = 29) was 83% (95% CI, 67%-94%). The numbers of patients with other pairings of donor types and performance status were too few to make statistical comparisons.

Age at transplantation, patient and donor sex, sex mismatch, patient-donor cytomegalovirus status, donor-recipient ABO compatibility, number of red blood cell transfusions received before transplantation, time from diagnosis to transplantation, use of a total body irradiation–based conditioning regimen, nucleated cell dose of the graft, year of transplantation, and use of growth factors after transplantation were not associated with survival. Additional analysis using lower and higher transfusion number cutoffs (<10 versus ≥10 and <50 versus ≥50 units of blood) also failed to demonstrate a significant survival difference (data not shown).

Of the 38 surviving patients with a median follow up of 11 years (range, 1-14 years), 37 have a normal white blood cell count of ≥4.0 × 10^9/L. Of these 38 patients, 25 are known to be red blood cell transfusion independent, and transfusion data are not available on the remaining 13 patients.

Causes of death. Twenty-three (38%) of 61 patients died after transplantation. Of these, 11 died within the first 100 days after transplantation; the probability of mortality at 100 days after transplantation was 18% (95% CI, 10%-29%). Causes of death are shown in Table 5.

DISCUSSION

This study describes long-term outcomes of patients with DBA after allogeneic BMT. The relatively large patient number, unselected nature of the group, and multicenter and multinational origin of study subjects strengthen the conclusions of the study. The 76% (95% CI, 59%-86%) 3- year survival of HLA-identical sibling donor transplant recipients in our study is similar to the 66% to 87% reported in the literature [8,20,21]. In general, more favorable outcomes were seen in patients with a better performance status at the time of transplantation and in recipients of matched sibling donor transplants.

We found a 9% incidence of nonengraftment. This is similar to that seen in similar nonmalignant hematologic disorders such as thalassemia, aplastic anemia, and sickle cell disease, in which an approximately 10% risk of graft failure has been reported [28,29]. The number of transfusions before transplantation was significantly correlated with the speed of neutrophil and platelet recovery. Patients who received <50 transfusions before transplantation were more likely to have neutrophil recovery by day 28 and platelet recovery by day 60 than patients who received ≥50 transfusions. However, this did not affect survival (data not shown).

In patients with thalassemia, improved outcomes have been shown when transplantation is performed at a younger age, before multiple transfusions lead to iron overload. The number of patients in our study was too small to evaluate this possibility. Even though we did not find a correlation between more transfusions and survival, iatrogenic iron overload might have contributed to performance status deterioration. Moreover, we do not have data on serum ferritin. A large sample that

Table 4. *Significant Variables Associated with Survival among Patients Who Underwent Allogeneic Bone Marrow or Peripheral Blood Transplantation for Diamond-Blackfan Anemia*

End Point	No. Evaluated	Probability (95% CI)*	P Value†
100-d survival			
Karnofsky/Lansky score			<.001
≥90	41	93 (79–98)	
<90	19	63 (38–80)	
Type of donor			.120
HLA-identical sibling	41	88 (73–95)	
Other	20	70 (45–85)	
Overall survival at 1 y			
Karnofsky/Lansky score			.020
≥90	41	78 (62–88)	
<90	19	47 (24–67)	
Type of donor			.010
HLA-identical sibling	41	78 (62–88)	
Other	20	45 (23–65)	
Overall survival at 3 y			
Karnofsky/Lansky score			.011
<90	19	42 (20–62)	
≥90	41	75 (59–86)	
Type of donor			.005
HLA-identical sibling	41	76 (59–86)	
Other	20	39 (19–60)	

CI indicates confidence interval.
*Survival was calculated by using the Kaplan-Meier product-limit estimate.
†Pointwise *P* value.

includes a cohort of untransfused patients before transplantation is required to specifically evaluate the effect of transfusions on survival and engraftment in these patients. However, such a study is unlikely to occur because transplantation is often withheld until patients are refractory to other therapies, and by that time they are usually transfusion dependent. All patients in our series had received prior red blood cell transfusions.

Recipients of alternative donor transplants had worse survival compared with HLA-identical sibling donor transplant recipients (76% versus 39%; $P = .005$). Other studies have also reported similar results after alternative donor transplantations (87% versus 14%) [21]. In our series, alternative donor transplant recipients were more likely to be older, to have received a total body irradiation–containing conditioning regimen, and to have had a longer time from diagnosis to transplantation. These factors may have contributed to the worse outcome of these patients.

Potential related donors may require additional evaluation because some cases initially thought to be sporadic were later deemed familial DBA [30]. An increased erythrocyte amine deaminase, fetal hemoglobin level, or macrocytosis may be the only phenotypic abnormality in the siblings [31]. Even more disconcerting is that obligate heterozygotes may exhibit a completely silent phenotype [32]. The consequence of using such a sibling as a donor is unknown. A single report described a DBA patient who did not engraft after receiving a graft from his sister, who had high serum levels of erythrocyte amine deaminase [33]. Although the rate of nonengraftment in our series is not high and is similar to that with other nonmalignant hematologic disorders, we cannot be certain whether any instances

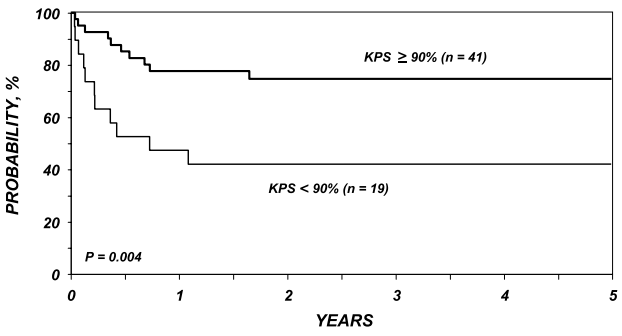

Figure 1. Probability of overall survival after bone marrow transplantation for Diamond-Blackfan anemia, by Karnofsky performance score (KPS) before transplantation.

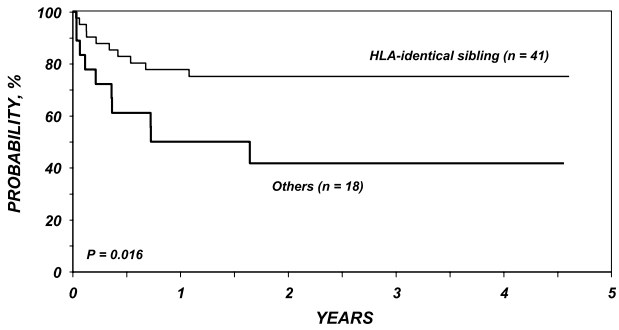

Figure 2. Probability of overall survival after bone marrow transplantation for Diamond-Blackfan anemia, by type of donor.

Table 5. *Causes of Death among Patients Who Underwent Allogeneic Transplantation for Diamond-Blackfan Anemia (n = 23)*

Cause of Death	n (%)
Graft failure	**6 (27)**
GVHD	**1 (4)**
Interstitial pneumonia	**3 (13)**
Infection	**7 (31)**
Organ failure	**2 (9)**
Hemorrhage	**1 (4)**
Cerebral infarction	**1 (4)**
Seizures and hypoxia	**1 (4)**
Other	**1 (4)**

GVHD indicates graft-versus-host disease.

The causes of death for the first 100 days were graft failure (n = 4), GVHD (n = 1), interstitial pneumonia (n = 3), organ failure (n = 1), hemorrhage (n = 1), and seizures and hypoxia (n = 1).

could be attributed to the use of an affected donor. This suggests that caution should be exercised in selection of a related donor. Related donors should be evaluated for erythrocyte amine deaminase, fetal hemoglobin, macrocytosis, and physical abnormalities consistent with DBA. RPS19 mutation analysis should be performed in all DBA patients, and, when positive, their prospective donors should be evaluated to ensure absence of the mutation.

With a median follow-up of >10 years, these patients had Karnofsky performance scores of 90 or 100. Even though performance status is at best a rough measure of quality of life, these scores suggest that long-term survivors do not experience excess morbidity after transplantation. In addition, engraftment has been sustained in surviving patients, thus indicating a good hematologic response to transplantation. None of these patients was reported to have developed a malignancy after transplantation.

All patients except 1 in this series received conventional, cyclophosphamide-based conditioning regimens. Nonmyeloablative or reduced-intensity conditioning regimens may decrease transplant-related morbidity and mortality, but this remains to be proven. Case reports of successful nonmyeloablative transplantations in DBA are encouraging [34,35], but further studies with larger patient numbers are needed to critically evaluate its role. We conclude that allogeneic BMT can result in long-term survival for patients with DBA. Early transplantation before patients develop transfusion-related iron overload or other comorbidities might improve outcomes. Although HLA-matched sibling donors are generally preferred over alternative donors, one must remain alert to the possibility of siblings with a hematologically silent DBA phenotype [33]. Unrelated donor transplants should be considered in selected patients.

ACKNOWLEDGMENTS

Supported by Public Health Service grant no. U24-CA76518 from the National Cancer Institute, the National Institute of Allergy and Infectious Diseases, and the National Heart, Lung and Blood Institute; Agency for Healthcare Research and Quality; and grants from Aetna; AIG Medical Excess; Allianz Life/Life Trac; American Red Cross; American Society of Clinical Oncology; Amgen, Inc.; an anonymous donation to the Medical College of Wisconsin; AnorMED, Inc.; Aventis Pharmaceuticals; Baxter Healthcare Corp.; Baxter Oncology; Berlex Laboratories, Inc.; Biogen IDEC, Inc.; Blue Cross and Blue Shield Association; The Lynde and Harry Bradley Foundation; BRT Laboratories, Inc.; Cedarlane Laboratories Ltd.; Celgene Corp.; Cell Pathways; Cell Therapeutics, Inc.; CelMed Biosciences; Centocor, Inc.; Cubist Pharmaceuticals; Dynal Biotech ASA; Edwards Lifesciences RMI; Endo Pharmaceuticals, Inc.; Enzon Pharmaceuticals, Inc.; ESP Pharma; Excess, Inc.; Fujisawa Healthcare, Inc.; Gambro BCT, Inc.; Genzyme; GlaxoSmithKline, Inc.; Human Genome Sciences; ICN Pharmaceuticals, Inc.; ILEX Oncology; Kirin Brewery Company; Ligand Pharmaceuticals, Inc.; Eli Lilly and Company; Nada and Herbert P. Mahler Charities; Merck & Company; Millennium Pharmaceuticals; Miller Pharmacal Group; Milliman USA, Inc.; Miltenyi Biotec; The Irving I. Moskowitz Foundation; National Leukemia Research Association; National Marrow Donor Program; NeoRx Corporation; Novartis Pharmaceuticals, Inc.; Novo Nordisk Pharmaceuticals; Ortho Biotech, Inc.; Osiris Therapeutics, Inc.; PacifiCare Health Systems; Pall Medical; Pfizer U.S. Pharmaceuticals; Pharmametrics; Pharmion Corp.; Protein Design Labs; QOL Medical; Roche Laboratories; Schering AG; StemCyte, Inc.; StemCell Technologies, Inc.; Stemco Biomedical; StemSoft Software, Inc.; SuperGen, Inc.; Sysmex; THERAKOS, a Johnson & Johnson Co.; University of Colorado Cord Blood Bank; Upside Endeavors; ViaCell, Inc.; ViaCor Biotechnologies; WB Saunders Mosby Churchill; Wellpoint Health Network; and Zymogenetics, Inc. The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

APPENDIX I

In addition to the authors, other members of the International Bone Marrow Transplant Registry Working Committee on Non-Malignant Marrow Disorders who participated in the study included the following: S.E. Ball, MD, St. George's Hospital Medical School, London, United Kingdom; B.M. Camitta, MD, Medical College of Wisconsin, Milwaukee, WI; R.P. Gale, MD, PhD, Center for Advanced Studies in

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