



Diamond-Blackfan anaemia

Hematopoietic stem cell transplantation for Diamond Blackfan anemia: a report from the Diamond Blackfan Anemia Registry

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Summary:

The Diamond Blackfan Anemia (DBA) Registry of North America is a detailed database of patients with DBA from the United States and Canada. To date, 354 patients have been registered. From this database an analysis of the outcome of hematopoietic stem cell transplantation for DBA was undertaken. Of the 20 transplanted patients who met criteria for the diagnosis of DBA, eight underwent an allogeneic HLA-matched sibling hematopoietic stem cell transplant (SCT) and 12 an alternative donor SCT. The median age at transplant for all patients was 6 years 2 months; 3 years 10 months vs 9 years 1 month for HLA-matched sibling and alternative donor SCT, respectively. All of the HLA-matched sibling transplants were done using a non-irradiation-containing regimen, whereas the majority of alternative donor transplants were performed using total body irradiation. The survival for HLA-matched sibling vs alternative donor transplant was 87.5% ± 11.7% vs 14.1% ± 12.1% at greater than 5 years from SCT ($P = 0.015$). The use of HLA-matched sibling SCT should be considered for all patients with suitable donors. However, alternative donor SCT in DBA must be approached cautiously, the potential for severe aplastic anemia (SAA) or hematopoietic malignancy not withstanding. *Bone Marrow Transplantation* (2001) 27, 381–386.

Keywords: Diamond Blackfan anemia; stem cell transplantation

Diamond Blackfan anemia (DBA) is a rare pure red cell aplasia, predominantly of infancy and childhood,¹ resulting from an intrinsic erythroid progenitor defect.² Ninety per cent of patients are diagnosed by 1 year of age. Recently one,³ of what appears to be multiple 'DBA genes',⁴ has been identified. The mainstay of treatment is corticosteroids, to which approximately 80% of the patients initially respond. The remaining 20% who are nonresponsive to

corticosteroids, and others, who may become nonresponsive or encounter significant corticosteroid-related toxic side-effects, are placed on a chronic red cell transfusion and deferoxamine chelation program. Both chronic corticosteroid therapy and chronic transfusion therapy may lead to a number of significant immediate and long-term complications.⁵ Thus, bone marrow transplantation has been explored as an alternative. The first 'successful' bone marrow transplant for DBA was reported in 1976.⁶ The patient died of interstitial pneumonitis on day +55, but hematopoietic engraftment from donor bone marrow confirmed DBA as a transplantable disease. Since the initial case, 50 additional transplants, virtually all from HLA-matched sibling donors, have appeared in the literature,^{7–24} the majority done prior to 1993. We now describe 20 stem cell transplants (SCT), 12 utilizing alternative donors, in DBA patients reported to the Diamond Blackfan Anemia Registry of North America (DBAR), all performed since 1993.

Patients and methods

The Diamond Blackfan Anemia Registry of North America was established in 1993 to collect demographic, laboratory and clinical data on DBA patients in the United States and Canada. Enrollment has been solicited through outreach to pediatric hematologists and family groups. After informed consent is obtained, patients are enrolled in the DBAR and complete a detailed questionnaire with the help of their physician(s). Physicians may enroll deceased patients posthumously without patient identifiers. Additional specific information is provided by a review of available medical records. Pathology reports are reviewed for cases of malignancy reported to the DBAR. Telephone interviews are periodically conducted with the patient and/or their family and their physician(s) in order to clarify and update information. Patients are excluded from the data analysis if they do not meet established diagnostic criteria for DBA as described by Diamond *et al.*²⁵ As of 31 December 1999, 354 patients have been enrolled in the DBAR. Of these, 21 patients were reported to the DBAR as having had a hematopoietic stem cell transplant. All SCT were performed after 1993 at either a Pediatric Oncology Group or Children's Cancer Group approved stem cell transplant center. Twenty of these patients met established criteria for

the diagnosis of DBA.²⁵ One patient was excluded due to severe neutropenia at birth. Survival time was measured from the month of stem cell transplant to the last follow-up evaluation with only death counted as an event. Patients who were alive at their most recent follow-up were censored at that date. Comparisons of survival were made using the log rank method. Actuarial survival curves were constructed using the Kaplan–Meier method²⁶ with SPSS 10.0 software (Windows 98).

Results

Eight patients were transplanted using HLA-matched sibling donors. Of the 12 alternative donor SCT, two were from a mismatched relative and 10 were from unrelated donors. The median age for all patients at transplant was 6 years 2 months (range, 1 year 4 months to 23 years 3 months); 3 years 10 months (range, 1 year 6 months to 21 years 4 months) vs 9 years 1 month (range, 1 year 4 months to 23 years 3 months) for HLA-matched sibling and alternative donor SCT, respectively (Table 1). There was a trend towards alternative donor transplants being performed at an older age than HLA-matched sibling transplants. However, the difference in age was not statistically significant ($P = 0.164$).

The major indication for SCT was transfusion-dependence. Seven of the eight allogeneic HLA-matched sibling SCT were transfusion-dependent at the time of SCT. One patient remained responsive to steroids at the time of SCT. Three of the seven transfusion-dependent patients were steroid nonresponsive from diagnosis, whereas four were initially steroid responsive. Of the steroid responsive patients, two required cessation of corticosteroid therapy due to significant steroid-related side-effects, one became steroid nonresponsive and one could not be weaned to an acceptable steroid dose. One steroid nonresponsive patient developed SAA. All alternative donor SCT patients were transfusion-dependent at the time of SCT. Three of 12 were initially steroid nonresponsive, one of these developed transient neutropenia and thrombocytopenia. Of the nine initially steroid responsive patients, six discontinued steroid therapy because of intolerable side-effects, and one of these evolved to SAA; three patients became steroid nonresponsive (Table 1).

Of the eight HLA-matched sibling transplants, seven were done using bone marrow (BM) and one using umbilical cord blood (UCB) as the stem cell source. Of the 12 alternative donor transplants, eight were done using BM and four using UCB (Table 1). Of the eight alternative donor SCT performed utilizing BM two were from partially matched relatives. The remaining six were from six antigen HLA-matched unrelated donors as determined serologically for class I and molecularly for class II in four (UPIN 223, 231, 248 and 260) and molecularly for class I and II in two (UPIN 269 and 291). All of the HLA-matched sibling SCT were done using a nonirradiation-containing preparative regimen, whereas the majority of alternative donor SCT were performed using myeloablative chemotherapy and total body irradiation. The vast majority of patients received a cyclosporine-containing graft-versus-host disease (GVHD) prophylaxis regimen (Table 2).

Seven of the HLA-matched sibling SCT are alive and well; a 21-year-old patient with severe iron overload and chronic hepatitis C (UPIN 84) died on day +71 from complications of GVHD. One heavily transfused patient (UPIN 216) suffered an intracranial hemorrhage as a consequence of platelet transfusion-refractory thrombocytopenia. There were two related alternative donor SCT. One was done using a haploidentical related sibling donor (UPIN 99); the patient died on day +262 of a pulmonary hemorrhage, following graft rejection. The second was done using a five of six HLA-matched mother (UPIN 121); the patient died on day +265 from complications of hepatitis B. Of the remaining 10 alternative donor SCT from either unrelated BM or UCB, only three are alive (Table 1). Seven died from GVHD and/or transplant-related toxicity and one (UPIN 200) from metastatic osteogenic sarcoma on day +1571 post SCT (Table 2). The actuarial survival for HLA-matched sibling and alternative donor SCT is $87.5\% \pm 11.7\%$ at 77.2 months and $14.1\% \pm 12.1\%$ at 61.9 months ($P = 0.015$), respectively (Figure 1). If the death from osteogenic sarcoma (UPIN 200) is considered to be non-transplant related,²⁷ then the survival for alternative donor SCT (Figure 1) is $28.1\% \pm 13.7\%$ ($P = 0.025$).

Discussion

Since 1951, corticosteroids have been the mainstay of treatment for DBA.²⁸ For those patients who fail this modality, either as a consequence of nonresponsiveness or unacceptable toxicity, chronic red cell transfusions and deferoxamine chelation have been the treatments of choice.

Since the first successful treatment of an immunodeficient patient using HLA-matched allogeneic sibling marrow transplantation in 1968,²⁹ hematopoietic stem cell transplantation has been utilized with variable success in a variety of oncologic and acquired or genetic hematologic and immunologic diseases. The first such transplant for Diamond Blackfan anemia was performed by August *et al* in 1976.⁶ Donor engraftment in this case confirmed DBA to be a disorder for which transplantation is feasible. Over the past two decades additional selected case reports have been cited in the literature.^{7–18,20–23} The majority of these transplants were performed using HLA-matched sibling donors. As well, a series of 10 patients (eight of 10 from HLA-matched allogeneic siblings) has been reported by the International Bone Marrow Transplantation Registry¹⁹ and 13 transplants (11 of 13 from HLA-matched allogeneic siblings) were compiled by the French registry.²⁴ Since its inception in 1993, 354 patients have been enrolled in the DBAR. This report represents an unselected compilation of 20 patients enrolled in the DBAR meeting the diagnostic criteria for DBA and having received a stem cell transplant. Most patients were transplanted as an alternative to chronic transfusion.

In a 1998 review of SCT in DBA by Alter³⁰ that included 35 of 37 cases^{7–23} from the literature, the projected actuarial survival for SCT, done utilizing predominantly allogeneic HLA-matched related donor-derived stem cells (33 siblings, one mother and one unrelated donor transplant), was 66%. Thus results from the DBAR for HLA-matched

Table 1 Stem cell transplantation in DBA (*n* = 20)

UPIN	Date of SCT	Age at transplant	Stem cell source	Donor-Recipient HLA relationship	Outcome	Indication for SCT/Comments
52	2/17/95	4yr 11mo	UCB	6/6-Allo sib	Alive	SAA, SNR, seizure disorder
84	2/10/93	21yr 4 mo	BM	6/6-Allo sib	Dead d+61	Severe iron overload, unable to wean steroids chronic hepatitis C
167	2/2/98	6yr 11 mo	BM	6/6-Allo sib	Alive	Steroid SE – poor growth
203	5/23/94	1yr 6 mo	BM	6/6-Allo sib	Alive	Became SNR, hypogammaglobulinemia
216	4/26/93	6yr 1mo	BM	6/6-Allo sib	Alive	SNR
226	9/10/93	2yr 8mo	BM	6/6-Allo sib	Alive	SNR
227	2/22/97	2yr	BM	6/6-Allo sib	Alive	Steroid SE – fluid retention, mood swings
229	11/1/96	1yr 8mo	BM	6/6-Allo sib	Alive	Steroid SE – severe hypertension
99	6/24/94	15yr 4mo	BM	3/6-Mismatched sib	Dead d+267	Steroid SE – aseptic necrosis of femoral heads
121	11/18/98	17yr 8mo	BM	5/6 Mother	Dead d+265	Became SNR
172	6/26/96	6yr 3mo	UCB	6/6-Unrelated	Dead d+62	SNR
188	5/24/96	2yr 5mo	UCB	4/6-Unrelated	Dead d+71	SNR, transient neutropenia, thrombocytopenia
200	5/10/95	1yr 4mo	UCB	5/6-Unrelated	Dead d+1571	SNR
223	9/1/94	3yr 5mo	BM	6/6-Unrelated	Dead d+599	Became SNR, severe iron overload
231	12/12/97	18yr 4mo	BM	6/6-Unrelated	Dead d+59	Steroid SE – poor growth; multiple CVA's, seizures
244	7/23/97	23yr 3mo	UCB	4/6-Unrelated	Alive	Steroid SE – poor growth; transverse sinus thrombosis, iron overload
248	10/2/98	8yr 5mo	BM	6/6-Unrelated	Dead d+114	Steroid SE – poor growth; neutropenia
260	7/27/94	13yr 5mo	BM	6/6-Unrelated	Alive	Steroid SE – pseudotumor cerebri
269	11/30/98	9yr 8mo	BM	6/6-Unrelated	Dead d+223	Became SNR, neutropenia, steroid SE – poor growth
291	6/10/99	5yr 11mo	BM	6/6-Unrelated	Alive	SAA, steroid SE – pathologic fracture

UCB = umbilical cord blood; BM = bone marrow; d = day; SAA = severe aplastic anemia; SE = side-effects; SNR = steroid non-responsive.

related SCT appear superior to those of earlier cases and comparable to those reported to the French registry.²⁴ In general, favorable SCT outcomes are most likely if the patient is in good health at the time of SCT without complications of iron overload. Indeed, of the eight patients receiving an HLA-matched sibling SCT, there was only one death, that being in an older, heavily iron-overloaded patient with hepatitis C. Of the remaining seven patients, all are alive and well with no evidence of GVHD. One heavily transfused patient, however, has significant neurologic sequelae as a consequence of a thrombocytopenia-associated intracranial hemorrhage due to platelet allo-sensitization. Improvements in supportive care, GVHD prophylaxis and infection control have resulted in a marked decrease in HLA-matched related SCT transplant-related morbidity and mortality. Thus, sibling SCT should be considered at a young age, prior to the development of significant allosensitization or iron overload, for those DBA patients with available HLA-matched related donors.

The outcomes for alternative donor SCT are significantly inferior to those performed using HLA-matched sibling donors, supporting a more conservative approach. Of the 12 patients who received an alternative donor SCT, only three are presently alive. For the most part the patients receiving either an HLA-matched sibling or an alternative SCT were similar with regard to age, transfusion status, and clinical condition. The difference in outcome, therefore, appears to be primarily a consequence of the donor-recipient relationship and the differences in preparative regimen, graft-versus-host disease prophylaxis and treatment, and supportive care resulting from those relationships. Thus, as

opposed to Fanconi anemia,³¹ Shwachman Diamond syndrome³² and dyskeratosis congenita,³³ DBA in itself does not appear to pose a particular risk for allogeneic matched sibling SCT.

In addition, the differences in transplant outcome between HLA-matched sibling transplant and alternative donor transplant does not appear to be a consequence of the stem cell source. In particular, umbilical cord blood (UCB) was utilized in one HLA-sibling transplant and in four alternative donor transplants. The HLA-matched sibling transplant performed using the UCB was uneventful. Although all alternative donor transplants performed utilizing UCB engrafted, three of the four died. These deaths were due to acute GVHD with infection, acute GVHD with veno-occlusive disease and metastatic osteogenic sarcoma on day +62, +71, and +1571, respectively.

Dianzani *et al*³⁴ point out the similarity between DBA and thalassemia major and suggest that similar criteria for SCT should be applied in both. Indeed, the ideal thalassemia major SCT candidate is a young patient who is minimally transfused or at least in good iron balance, with no evidence of significant hepatic damage, transplanted from an HLA-identical sibling donor. Our data support that observation with the caveat that the true incidence of severe aplastic anemia,³⁵ myelodysplasia, and leukemia²⁷ in DBA patients is unknown.

As DBA is the result of an intrinsic hematopoietic progenitor defect the recent finding of severe aplastic anemia, reported in the literature,³⁵ and in two of the transplanted patients in this series (one additional patient had persistent thrombocytopenia), is not unexpected. The finding, how-

Table 2 Stem cell transplantation in DBA (n = 20)

UPIN	Pre-SCT status	Donor-Recipient HLA relationship/ stem cell source	Conditioning regimen	Acute GVHD prophylaxis	Outcome	Cause of death
52	SNR, Tx-dep	6/6-Allo sib/UCB	Bu/Cy	MTX	Alive	
84	SR, Tx-dep	6/6-Allo sib/BM	Bu/Cy	CsA/ATG	Dead d+61	Adenovirus bronchiolitis, acute GVHD – gut, grade not specified
167	SR	6/6-Allo sib/BM	TT/Cy	CsA/MTX	Alive	
203	SR, Tx-dep	6/6-Allo sib/BM	TT/Cy	CsA/MTX	Alive	
216	SNR, Tx-dep	6/6-Allo sib/BM	Bu/Cy/ATG	CsA	Alive	
226	SNR, Tx-dep	6/6-Allo sib/BM	Cy/ATG	CsA/MTX	Alive	
227	SR, Tx-dep	6/6-Allo sib/BM	Bu/Cy/ATG	CsA/Cort	Alive	
229	SR, Tx-dep	6/6-Allo sib/BM	Bu/Cy	CsA/MTX	Alive	
99	SR, Tx-dep	3/6-Mismatched sib/BM	TBI/Cy/Ara-C/MP	T cell depletion/ CsA/ATG/Cort	Dead d+267	Graft rejection, pulmonary hemorrhage
121	SR, Tx-dep	5/6 Mother/BM	Bu/Cy	CsA/MTX	Dead d+265	Fulminate hepatitis B
172	SNR, Tx-dep	6/6-Unrelated/UCB	TBI/TT/Cy	CsA/MTX/ATG	Dead d+62	Pulmonary aspergillosis, cerebral abscess, acute GvHD – skin, grade I/II
188	SNR, Tx-dep	4/6-Unrelated/UCB	Bu/Cy/ATG	CsA/Cort	Dead d+71	Acute GVHD – gut, grade IV, veno-occlusive disease
200	SNR, Tx-dep	5/6-Unrelated/UCB	TBI/Bu/Cy	CsA/MTX/Cort	Dead d+1571	Metastatic osteosarcoma
223	SR, Tx-dep	6/6-Unrelated/BM	Bu/Cy/VP/ATG	CsA/Cort	Dead d+599	Acute GVHD – gut, grade IV, chronic GVHD – skin, gut; ARDS
231	SR, Tx-dep	6/6-Unrelated/BM	TBI/Cy/ATG	CsA	Dead d+59	Acute GVHD – gut, grade IV; CNS bleed, interstitial pneumonitis
244	SR, Tx-dep	4/6-Unrelated/UCB	Bu/Cy/ATG	CsA/Cort	Alive	
248	SR, Tx-dep	6/6-Unrelated/BM	TBI/Bu/Cy	T-cell depletion/ CsA/ATG/Cort	Dead d+114	Primary EBV infection, encephalitis
260	SR, Tx-dep	6/6-Unrelated/BM	TBI/Cy/Ara-C/Cort	T-cell depletion/ CsA/ATG/Cort	Alive	
269	SR, Tx-dep	6/6-Unrelated/BM	TBI/Bu/Cy	CsA	Dead d+223	Candidal sepsis
291	SR, Tx-dep	6/6-Unrelated/BM	TBI/Cy/ATG	CsA	Alive	

SNR = initially steroid nonresponsive; SR = initially steroid responsive; Tx-dep = transfusion dependent; Bu = busulfan; Cy = cyclophosphamide; TT = thiotepa; ATG = anti-thymocyte globulin; TBI = total body irradiation; Ara-C = cytosine arabinoside; VP = VP16 (etoposide); MTX = methotrexate; CsA = cyclosporine; Cort = corticosteroid; UCB = umbilical cord blood; BM = bone marrow; ARDS = adult respiratory distress syndrome.

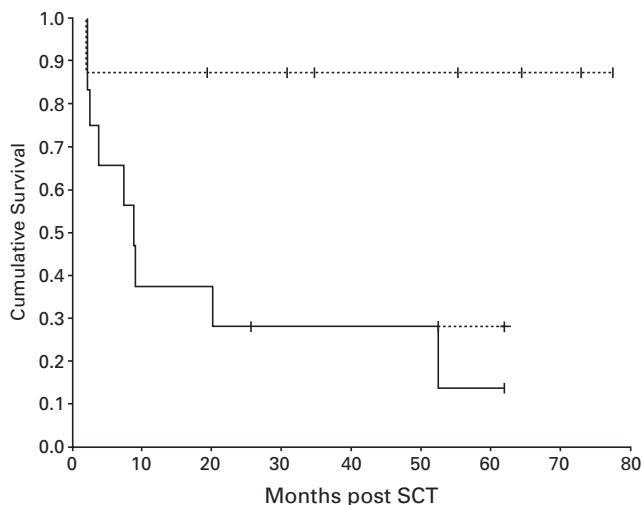


Figure 1 Kaplan–Meier analysis of survival in DBA patients undergoing HLA-matched sibling (-----) vs alternative donor stem cell transplant. Alternative donor SCT are presented without (—) and with (.....) the death from osteogenic sarcoma censored.

ever, of osteogenic sarcoma in a DBA patient less than 5 years of age strongly supports the existence of a previously unknown association between the two entities.²⁷ The extent to which the preparatory regimen of total body irradiation, busulfan and cyclophosphamide contributed to the development of osteogenic sarcoma as a post-SCT complication in this patient cannot be determined.

Another confounding variable complicating the decision to perform SCT is the observation that approximately 15–25% of DBA patients may enter a durable spontaneous remission. This may occur both in those patients who are steroid responsive, as well as those who are transfusion dependent, with the majority occurring prior to the 8th year of life.⁵

In summary, allogeneic sibling stem cell transplantation in young DBA patients without significant iron overload or organ dysfunction is a reasonable alternative to corticosteroid or transfusion therapy and, as well, obviates the risk of trilineage hematopoietic failure or hematologic malignancy. There must be a note of caution regarding allogeneic donor selection. Recently a significant number of apparently hematologically normal family members of DBA patients have been found to have a silent DBA phenotype

by virtue of macrocytosis, elevated fetal hemoglobin and/or erythrocyte adenosine deaminase activity.³⁶ An allogeneic SCT inadvertently using one such donor, predictably resulted in graft failure.³⁷ Allogeneic related donor evaluations must explore this possibility.

In contrast to HLA-matched sibling SCT alternative donor transplantation, especially in light of a reasonable likelihood of spontaneous remission, should be considered on a case-by-case basis when individual circumstances justify the risk. Improvements in the control of GVHD as well as more precise high resolution HLA typing and the availability of larger donor pools should lead to improved outcomes for transplants utilizing alternative donor sources. The risk of non-hematologic malignancy in patients with DBA²⁷ and the role of SCT, particularly with radiation-based preparatory regimens,³⁸ needs to be investigated. As such, alternative non-SCT approaches and new methods for achieving hematopoietic chimerism, without aggressive myeloablation, are being developed and should be explored in selected patients with Diamond Blackfan anemia.

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