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Brief Article

Stem Cell Transplantation for Diamond–Blackfan Anemia. A Retrospective Study on Behalf of the Severe Aplastic Anemia Working Party of the European Blood and Marrow Transplantation Group (EBMT)

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A B S T R A C T

Data on stem cell transplantation (SCT) for Diamond–Blackfan Anemia (DBA) is limited. We studied patients transplanted for DBA and registered in the EBMT database. Between 1985 and 2016, 106 DBA patients (median age, 6.8 years) underwent hematopoietic stem cell transplantation from matched-sibling donors (57%), unrelated donors (36%), or other related donors (7%), using marrow (68%), peripheral blood stem cells (20%), both marrow and peripheral blood stem cells (1%), or cord blood (11%). The cumulative incidence of engraftment was 86% (80% to 93%), and neutrophil recovery and platelet recovery were achieved on day +18 (range, 16 to 20) and +36 (range, 32 to 43), respectively. Three-year overall survival and event-free survival were 84% (77% to 91%) and 81% (74% to 89%), respectively. Older patients were significantly more likely to die (hazard ratio, 1.4; 95% confidence interval, 1.06 to 1.23; $P < .001$). Outcomes were similar between sibling compared to unrelated-donor transplants. The incidence of acute grades II to IV of graft-versus-host disease (GVHD) was 30% (21% to 39%), and the incidence of extensive chronic GVHD was 15% (7% to 22%). This study shows that SCT may represent an alternative therapeutic option for transfusion-dependent younger patients.

INTRODUCTION

Diamond–Blackfan anemia (DBA) is a congenital pure red cell aplasia, secondary to genetic defects of ribosomal proteins. It usually, but not exclusively, presents within the first year of life and can be associated with congenital abnormalities, as well as increased risk for cancer, mostly solid tumors. Some patients are successfully treated with steroids, but many of them remain dependent with unacceptable side effects, or they do not respond. Hematopoietic stem cell transplantation (HSCT) represents the only curative option for the hematological features of this disease. The reported studies show an improvement in overall survival (OS) over time (45% to 91%) that was more evident in unrelated donors as the source of stem cells, such that OS increased from 19% to 92% [1-5]. The same studies show better results in patients younger than 10 years of age and transplanted after the year 2000. In this retrospective study, we describe the outcomes of HSCT of the largest reported cohort of patients with DBA included in the EBMT database.

PATIENTS AND METHODS

Data from patients of any age who underwent HSCT for DBA between 1985 and 2016 and were registered in the EBMT database were analyzed. Details on transplant procedures were obtained from the database, and the patients' clinical information was collected by a specific disease-oriented questionnaire distributed to the participating centers. Engraftment was defined as the first date of a neutrophil count $\geq 0.5 \times 10^9$/L for at least 3 consecutive days. Primary and secondary graft failure were defined as neutrophil count never reaching $\geq 0.5 \times 10^9$/L and as a decrease in their count to a lower level after initial engraftment, respectively. Iron overload was defined as ferritin serum level > 1000 mg/dL and/or the presence of pathological liver iron concentration by magnetic resonance imaging.

The overall survival (OS) and event-free survival (EFS), defined as survival without graft loss, relapse, malignancy, or a second transplant, were calculated using the Kaplan–Meier product limit estimation method; differences in subgroups were assessed by the log-rank test. The reverse Kaplan–Meier method was used to estimate the median follow-up. Cumulative incidences of acute graft-versus-host disease (aGVHD), chronic graft versus host disease (cGVHD), and graft failure were analyzed separately in a competing risks framework, and subgroup differences were assessed by Gray's test. Competing events for graft failure and acute or chronic GVHD included second transplant, relapse, and death. In the corresponding figures, failure from any competing event is referred to simply as "failure." All estimates were reported with a corresponding 95% confidence interval (CI), and $P < .05$ was considered significant.

RESULTS AND DISCUSSION

Between 1985 and 2016, 106 patients (60 males, 57%; 46 females, 43%; mean age, 6.8 years; interquartile range [IQR], 3.7 to 11.2) underwent HSCT. Congenital malformations were present in 62% of patients. At the time of stem cell transplantation (SCT), patients had undergone a number of red blood cells transfusions: <20 (38% of cases) and >20 (62% of cases). Iron overload was present in 77% of patients, and previous treatments included steroids (93%), erythropoietin (11%), and leucine (5%). Transfusion dependency, iron overload, and evolution to aplasia represented the most common indications to transplant in 70%, 15%, and 7% of cases, respectively. Median hemoglobin, neutrophils, and platelet counts at SCT were 9.1 g/dL (IQR, 8 to 10.2), $1.8 \times 10^3/\mu$L (IQR, 1.3 to 2.9), and $285 \times 10^3/\mu$L (IQR, 147 to 353), respectively. Patient characteristics and transplant features are provided in Table 1. Median days to neutrophil and platelet engraftment were 18 (range, 16 to 20) and 36 (range, 32 to 43), respectively. Median follow-up was 68 months (range, 52 to 89). EFS and OS at 36 months were 81% (range, 74% to 89%) and 84% (range, 77% to 91%), respectively (Figure 1). Older patients were significantly more likely to die (hazard ratio [HR], 1.4; 95% CI, 1.06 to 1.23; $P< .001$). No significant differences on outcome were noted based on the year of transplant or the type of conditioning regimen. The median incidence of day 100 aGVHD (grades II to IV) was 30% (range, 21% to 39%), and the median incidence of extensive cGVHD at 36 months was 15% (range, 7% to 22%). Although not statistically significant, a higher incidence of extensive cGVHD was present in patients transplanted from unrelated donors (median 23%; range, 8% to 38%) compared to those who received stem cells from siblings (median 11%; range, 3% to 20%). Also associated with a significantly higher incidence of extensive cGVHD

Table 1
Patient and Transplant Characteristics

Characteristic	Value
Status at SCT	
Ferritin levels (ng/mL), median (IQR)	1272 (856–2230)
Age (yr), median (range)	6.8 (1-32)
Years of SCT, n (%)	
1985–2010	56 (53)
2011–2016	50 (47)
Donor type (missing 4), n (%)	
Identical sibling	58 (57)
Unrelated donor	37 (36)
Other relative	7 (7)
Sex match, recipient–donor (missing 6), n (%)	
Female–female	19 (19)
Female–male	24 (24)
Male–female	25 (25)
Male–male	32 (32)
CMV status, recipient–donor (missing 28), n (%)	
–/–	27 (35)
–/+	9 (12)
+/–	12 (15)
+/+	30 (38)
Stem cell source, n (%)	
Bone marrow	68 (64)
Peripheral blood	21 (20)
Cord blood	16 (15)
Bone marrow and peripheral blood	1 (1)
GVHD prophylaxis (missing 10), n	
Cyclosporin + MTX ± other	52
Cyclosporin + MTX + MMF ± other	2
Cyclosporin + MMF	13
Cyclosporin	19
Tacrolimus + MTX	1
Tacrolimus + MMF	3
Cyclosporin	4
MMF	1
MTX	1
Conditioning regimen (missing 8), n (%)	
Myeloablative	82 (84)
Busulfan-based	66 (80)
Busulfan	3 (5)
Busulfan–cyclophosphamide	47 (71)
Busulfan–fludarabine ± other	16 (24)
Treosulfan-based	16 (20)
Treosulfan–fludarabine	15 (93)
Treosulfan–cyclophosphamide	1 (7)
No myeloablative	16 (16)
Fludarabine-based	12 (75)
Cyclophosphamide	4 (25)
Chimerism, n	
Full	79
Mixed	5
Aplasia, not evaluated, or lost engraftment	5
Missing	17

CMV indicates cytomegalovirus; MTX, methotrexate; MMF, mycophenolate mofetil.

were iron overload (no, 0% versus yes, 24%; range, 12% to 35%) (P = .04) and number of previous red blood cell transfusions (<20 units, 4%; range, 0% to 12% versus ≥20 units, 24%; range, 11% to 36%) (P= .05) (Figure 1).

Sixteen patients died during follow-up due to infections (n = 7), GVHD (n = 4), organ failure (n = 2), other transplant-related causes (n = 2), or unknown causes (n = 1). Seven patients developed secondary malignancies (two solid tumors, one myelodysplasia, one non-Hodgkin lymphoma, two unknown) at a median of 67 months from HSCT

To the best of our knowledge, this is the largest reported cohort of patients transplanted for DBA, and it represents a significant number of cases reported after 2010 that show very good OS in patients < 10 years of age, independent of donor type.

The better outcome of younger children, already shown in previous reports [4], has been confirmed in this much larger cohort of patients, highlighting the importance of identifying the correct timing to undergo transplantation in the management of transfusion-dependent patients with DBA, especially considering that the desired outcomes continuously reduce with age. In fact, an earlier procedure may prevent the iron overload side-effects that are known to predispose to greater transplant-related toxicity [6]. Indeed, previous reports on patients transplanted for other disorders requiring regular transfusions, such as thalassemia or congenital dyserythropoietic anemia [7,8], have already shown that tissue damage secondary to iron overload greatly impairs the outcome. Although in our study the number of red blood cell transfusions and presence of iron overload did not have any impact on survival, they were significantly associated with a higher incidence of extensive cGVHD, suggesting that adequate chelation treatment during early phases of the disease and complete evaluation of iron overload before transplant are mandatory in patients with DBA.

It is worth noting that the good outcomes of DBA patients transplanted under the age of 10 years must be viewed with caution and might not represent an absolute indication per se for HSCT. Unfortunately, sufficient outcome data on patients regularly transfused and correctly chelated who did not receive a transplant are not available to compare with those undertaking HSCT. Indeed, according to the North American DBA Registry, OS at age greater than 40 years is 75% [3], and these results might be even higher in the future due to the improvement of supportive therapies and chelation treatments seen over the last few years. Moreover, in the setting of other constitutional marrow failure syndromes such as Fanconi anemia, the management of which also highlights the dilemma regarding the timing of transplantation, it has been shown that, for moderate cytopenia, the OS of transplanted and non-transplanted patients is similar [9]. This finding reinforces the fact that indication and the timing for HSCT in DBA patients may not be dictated by age per se but instead should be carefully weighted and tailored according to the status of each patient. The possibility of correcting the hemopoietic manifestations of the disease must be balanced against the risk of cGVHD, which, in another transfusion-dependent anemia such as thalassaemia, is known to be associated with a lack of normalization of quality of life [10], and it is possible that conditioning may exacerbate the risk of tumors.

Our study did not show any difference in terms of survival between transplants from siblings or unrelated donors, confirming the trend of improving outcomes over the years [2,3,5], which was clearly highlighted in a recent study on a German and French cohort of children and adolescents whose OS was > 90% [5]. In our cohort of patients, which also included adult patients, mostly transplanted after 2010, OS and EFS were both higher (>80%), independently of donor type. The good outcome of unrelated donor transplants is particularly important for congenital diseases, which reduce the

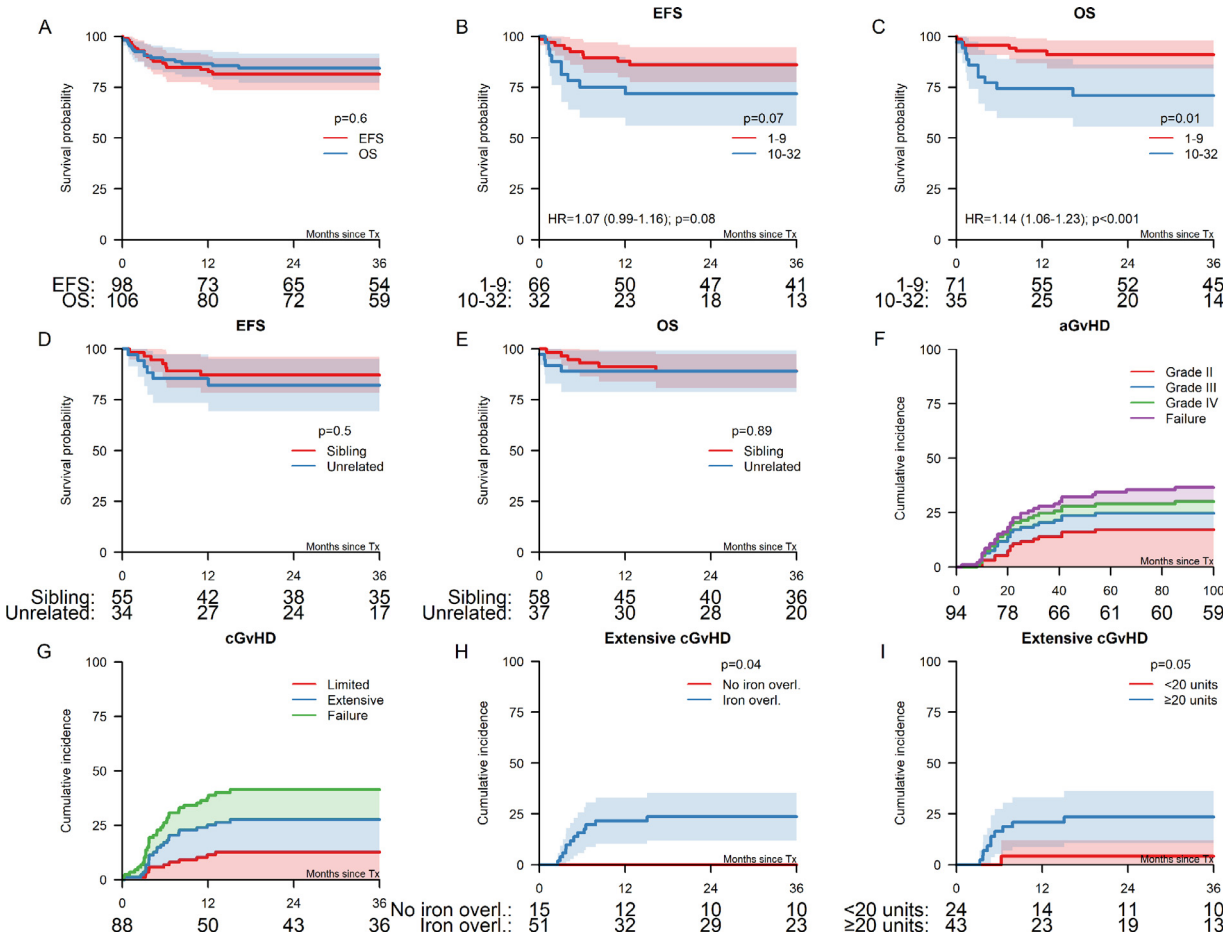

Figure 1. (A) EFS and OS. (B) EFS according to age. (C) OS according to age. (D) EFS according to donor type. (E) OS according to donor type. (F) Incidence of aGVHD. (G) Incidence of cGVHD. (H) Incidence of extensive cGVHD according to iron overload. (I) Incidence of extensive cGVHD according to number of transfusions. Failure indicates failure from any competing event

possibility of finding fully matched, non-affected family donors [8,11]. No significant differences were observed in OS by the type of stem cell source and conditioning regimen. Although previous reports have demonstrated that patients transplanted using cord blood had inferior outcomes [4,12], we did not observe any difference, although this may have been due to the small numbers.

More than 80% of patients underwent either a busulfan- or a treosulfan-based myeloablative conditioning regimen. Although in our study there was no significant difference with other regimens, these approaches and, in particular, the use of the less toxic drug treosulfan have recently been recommended by an international expert panel [13] and can represent a balanced choice to reduce transplant-related toxicity while maintaining a high engraftment rate. Treosulfan is particularly useful in constitutional marrow failure syndromes [14–16] that bear an intrinsic predisposition to malignancies, as is the case for DBA, which has a cumulative incidence of 20% by the age of 46 years [17], mostly due to solid tumors. In our cohort, 6% of patients developed post-transplant malignancies, and this figure is likely to further increase with follow-up time. Therefore, the use of a treosulfan-based conditioning regimen would be preferable in DBA patients, due to its reduced toxic effects.

In conclusion, the very good OS of patients undergoing transplant from both sibling and unrelated donors and the acceptable rate of cGVHD confirm that this procedure can be considered as an alternative option for young transfusion-dependent patients, after careful evaluation of patient-specific issues and needs.

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