TRANSPLANTATION

Outcome of patients with hemoglobinopathies given either cord blood or bone marrow transplantation from an HLA-identical sibling

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Key Points

- Patients with thalassemia major or sickle cell disease had excellent outcomes after both CBT and BMT from an HLA-identical sibling.
- Related cord blood transplantation is a suitable transplant option for patients with hemoglobinopathies.

We analyzed the outcomes of 485 patients with thalassemia major (TM) or sickle cell disease (SCD) receiving HLA-identical sibling cord blood transplantation (CBT, n = 96) or bone marrow transplantation (BMT, n = 389). Compared with patients given BMT, CBT recipients were significantly younger (median age 6 vs 8 years, *P* = .02), and were treated more recently (median year 2001 vs 1999, *P* < .01). A higher proportion of patients with TM belonging to classes II-III of the Pesaro classification received BMT (44%) compared with CBT (39%, *P* < .01). In comparison with patients receiving BMT (n = 259, TM; n = 130, SCD), those given CBT (n = 66, TM; n = 30, SCD) had slower neutrophil recovery, less acute graft-versus-host disease (GVHD) and none had extensive chronic GVHD. With a median follow-up of 70 months, the 6-year overall survival was 95% and 97% after BMT and CBT, respectively (*P* = .92). The 6-year disease-free survival (DFS) was 86% and 80% in TM patients after BMT and CBT, respectively, whereas DFS in SCD patients was 92% and 90%, respectively. The cell dose infused did not influence outcome of patients given CBT. In multivariate analysis, DFS did not differ between CBT and BMT recipients. Patients with TM or SCD have excellent outcomes after both HLA-identical sibling CBT and BMT. (*Blood*. 2013;122(6):1072-1078)

Introduction

Although improvements in supportive treatment have significantly improved the prognosis in thalassemia major (TM) and sickle cell disease (SCD) in developed nations,[1-3] hematopoietic stem cell transplantation (HSCT) still remains the only proven curative treatment of these disorders.[4-10] Since the first successful transplant performed in a child with TM by Thomas and colleagues in Seattle,[4] more than 1000 patients with TM or SCD have been cured by HSCT, in most cases performed using an HLA-identical sibling donor with bone marrow (BM) as the stem cell source.[11] More recently, BM transplantation (BMT) from an unrelated volunteer, selected by high-resolution molecular typing of class I and II HLA loci and stringent criteria of compatibility, also proved to be a possible alternative for selected patients with TM who lack a compatible family donor.[10,12-14]

In the last two decades, cord blood (CB) from an HLA-identical sibling increasingly is being used as an alternative source of hematopoietic cells for transplanting patients with either malignant or nonmalignant hematological diseases.[15-17] In particular, HLA-identical sibling CB transplantation (CBT) is associated with a low incidence of both acute and chronic graft-versus-host disease (GVHD), leading to a lower risk of fatal or life-threatening immune-mediated complications.[16] After anecdotal reports of successful CBT in children with TM or SCD,[18-20] a study from the Eurocord cooperative group, analyzing the outcome in 44 patients who had SCD or TM and were treated by CBT from a sibling donor, reported no fatal transplantation-related complications, suggesting that related CBT is a safe treatment for hemoglobin disorders.[21]

So far, no study has comparatively analyzed the outcome of patients with hemoglobinopathies transplanted with either BM or CB cells from an HLA-identical sibling. The aim of this analysis was to investigate, after long observation, whether patients with

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TM or SCD have different probabilities of benefiting from HLA-identical sibling CBT or BMT.

Patients and methods

Data concerning patient, donor, and disease characteristics, as well as transplantation outcome, were collected using a standardized questionnaire of the EUROCORD Registry for each patient enrolled into this study. This study included all patients with a diagnosis of either TM or SCD, who received family donor CBT between January 1994 and December 2005 in participating institutions. Patients given CB cells associated to BM cells were not included in this study. Centers reporting CBT for hemoglobinopathies to Eurocord were invited to report all cases of BMT for the same indications in the same time period to avoid any bias related to the period effect. CBTs performed in the United States were reported to the Sibling Donor Cord Blood Program in Oakland, California. The cohort of patients reported to the Eurocord registry included 411 patients; of them, 333 had received BMT and 78 CBT. Of these 411 patients, 310 had TM and 101 SCD, respectively. Seventy-four patients had received transplantation in North America and were reported to the Sibling Donor Cord Blood Program in Oakland, California: 56 of them were given BMT and 18 CBT; 16 and 58 were transplanted for TM or SCD, respectively. All patients included in this study were consecutive, and no patient was excluded from the analysis by the participating institutions. Transplantation was performed in 28 different Centers (see Appendix). The Eurocord registry collects the data on all consecutive CBT performed in Europe, and thus all patients given this type of allograft should have been reported to the Registry. Concerning the Oakland registry, it can be estimated that our cases represent around 37% of CBT performed for TM/SCD in North America. Forty-four of the 96 CBT recipients were reported in a previously published study (at that time with a median follow-up of 24 months), which analyzed outcomes and factors influencing outcome of patients with hemoglobinopathies given this type of allograft.[21] All patients with SCD given either CBT or BMT in North America have been previously reported (see also supplemental Table 1).

Parents of all patients included in this study were willing to have their children transplanted using an HLA-identical family donor; a detailed discussion of the risk/benefit ratio and of possible complications (including loss of fertility) of transplantation was held with the physicians before proceeding with HSCT. Exclusion criteria included the presence of left ventricular ejection fraction lower than 40%, positive serology for HIV, uncontrolled bacterial, viral or fungal infections, severe neurological, liver, lung, and renal function impairment, or a Karnofsky/Lansky score lower than 70. Informed consent was obtained from all patients' parents or their legal guardian in accordance with the Declaration of Helsinki. The study received approval by the local institutional review board/ethical committee of each participating Center.

Before transplantation, all TM patients were assigned to one of the 3 classes of risk proposed by Lucarelli et al[5] on the basis of adherence to a program of regular iron chelation therapy, and whether or not there was liver enlargement or evidence of portal fibrosis by liver biopsy.

In the majority of patients in Europe, CB was obtained from local cellular therapy laboratories or CB banks. The methods of collecting, cryopreserving, and storing CB varied among Centers. Usually, CB progenitors were thawed and washed following the procedure described by Rubinstein et al.[22]

In all donor-recipient pairs, histocompatibility was determined by serology for HLA-A and -B loci and by DNA typing for HLA-DRB1 locus.

Engraftment of donor cells was assessed through the use of molecular methods that detect informative polymorphisms in regions known to contain short tandem repeats (STR). Patients' peripheral blood mononuclear cells were analyzed for chimerism investigation. Individuals who exhibited more than a 95% donor profile by STR-PCR analysis were referred to as having full donor chimerism. Mixed chimerism was defined as greater than 5% recipient DNA. Graft failure was defined as undetectable DNA of donor origin on at least 2 occasions no less than 1 week apart.

BM or CB cells were infused after 48 and 72 hours following the last dose of cyclophosphamide (CY) and fludarabine (FLU), respectively.

Table 1. Patient, donor, and transplant characteristics of patients given BM or CBT for hemoglobinopathies

	BMT n = 389	CBT n = 96	*P* value
Median age at transplantation, y (range)	8.1 (0.7-24)	5.9 (2-20)	.02
Patient gender, male/female	200/189	48/48	.82
Median body weight, kg (range)	23 (7-71)	19 (10-60)	.01
Not available	3	0	
Donor gender, male/female	196/193	48/48	.87
Median donor age, y (range)	9.0 (0.2-30)	—	<.01
Diagnosis			
TM	259 (67%)	66 (69%)	.55
SCD	130 (33%)	30 (31%)	
Pesaro class for TM patients			
Class 1	86 (33%)	40 (61%)	<.01
Class 2	122 (31%)	23 (35%)	
Class 3	51 (13%)	2 (4%)	
Previous CNS involvement at time of transplantation in patients with SCD			
Yes	57 (56%)	16 (54%)	.83
No	73 (44%)	14 (46%)	
Patient HCMV serology			
Positive	142 (37%)	30 (35%)	.70
Negative	239 (63%)	61 (65%)	
Not available	8	5	
Median number of nucleated cells infused $\times 10^8$/kg of recipient body weight (range)	4.1 (0.1-46)	0.39 (1.5-14)	<.01
Not available	46	2	
ABO compatibility			
Compatible	248 (66%)	63 (70%)	.44
Minor incompatibility	48 (13%)	10 (12%)	
Major incompatibility	77 (21%)	22 (28%)	
Not available	17	1	
Median year of transplantation (range)	1999 (94-05)	2001 (94-05)	<.01
Conditioning regimen			
Bu/Cy	345 (89%)	53 (56%)	<.01
Bu/Cy/Flu	16 (4%)	5 (5%)	
Bu/Flu/TT	27 (7%)	21 (22%)	
Bu/Flu/	0	4 (4%)	
Bu/Cy/TT	0	10 (11%)	
Not available		1	
Use of ATG/ALG			
Yes	259 (67%)	49 (54%)	<.01
No	130 (33%)	43 (46%)	
Not available		5	
GVHD prophylaxis			
Scheme including MTX	296 (76%)	21 (30%)	<.01
Scheme without MTX	93 (24%)	73 (70%)	
Not available		2	

Bu, busulfan; CNS, central nervous system; HCMV, human cytomegalovirus; Treo, treosulfan.

Conditioning regimen

Details about patient and donor characteristics, conditioning regimen, GVHD prophylaxis, and the median number of BM and CB nucleated cells infused, are reported in Table 1. Patients transplanted with CB cells were more likely to receive FLU- and thiotepa (TT)-based regimens than were BMT recipients (see Table 1 for details).

GVHD prophylaxis

GVHD prophylaxis included cyclosporine-A in 99% and 97% of BMT and CBT recipients, respectively; a significantly greater proportion of patients given BMT also received short-term methotrexate (MTX) for GVHD prophylaxis (see Table 1 for details). A large proportion of CBT recipients (62%) were given a cyclosporine-A–only GVHD prophylaxis.

Antithymocyte globulin (ATG) or antilymphocyte globulin (ALG) was used more frequently in BMT than in CBT recipients (see also Table 1).

Definition of outcomes. The primary outcomes were: (1) *transplantation-related mortality* (TRM), defined as all causes of death related to the transplantation procedure; (2) *overall survival* (OS), which was measured by the time interval between the date of transplantation and the date of death or the date of last follow-up for surviving patients; (3) *disease-free survival* (DFS) defined as the time interval from transplantation to first event (either death or graft failure, whichever occurred first) or last follow-up for surviving patients; and (4) *event-free survival* (EFS) defined as the time interval from transplantation to first event (either death or graft failure, or occurrence of extensive chronic GVHD, whichever occurred first) or last follow-up for surviving patients. Other outcomes were: (a) *hematopoietic recovery*: neutrophil and platelet recovery were analyzed separately, and were defined by a neutrophil count greater than 0.5×10^9/L for three consecutive days, and an unsupported platelet count greater than 50×10^9/L for seven consecutive days, respectively. (b) *graft failure* was defined as either the absence of hematopoietic reconstitution of donor origin on day +60 after the allograft or second allogeneic HSCT (primary graft rejection), or as loss of donor cells after transient engraftment of donor-origin hematopoiesis, together with return to erythrocyte transfusion dependence for TM patients or together with reappearance of symptoms related to the original disorder for patients with SCD (secondary graft rejection). (c) *GVHD*: acute and chronic GVHD were diagnosed and graded in terms of severity at each transplant Centre according to the Seattle criteria.[23,24] Patients surviving for more than 14 and 100 days posttransplantation were evaluated for acute and chronic GVHD occurrence, respectively. Treatment for both acute and chronic GVHD was administered according to the protocols in use at each single Institution.

Statistical analysis. Analysis used 1 January 2012 as the report date, that is, the day at which the Centers locked up data on patient outcomes. Patients were censored at the time of death or at last follow-up. Probabilities of survival, DFS, and EFS were estimated by the Kaplan-Meier product-limit method and were expressed as percentage +/− standard error (SE). For calculation of DFS, the date when death, graft failure, or last follow-up occurred was captured, whereas for the calculation of EFS, the date when death, graft failure, extensive chronic GVHD, or last follow-up occurred was considered. The probabilities of neutrophil recovery, primary graft failure, and acute and chronic GVHD were expressed as cumulative incidence curves +/− SE, so as to adjust the analysis for competing risks.[25,26] In detail, the cumulative incidence of graft failure was defined as the probability of experiencing primary graft rejection at time *t*; death without developing graft failure was considered a competing event.

Univariate prognostic analyses used the log-rank test, testing the influence on each end point of patient characteristics (age, sex, body weight, HCMV serology, ABO compatibility), donor characteristics (age, sex, female/male donor-recipient combination), disease factors (original disease, class of risk for TM patients), and transplantation-related factors (number of nucleated cells collected per kg body weight, type of conditioning regimen, use of MTX for GVHD prophylaxis). Continuous covariates were encoded as binary covariates after dichotomization, using the median as cutoff. Multivariable prognostic analyses were performed for DFS, the principal end point, using Cox proportional regression model.[27] The following variables were included in the multivariate model: type of stem cell source, age at transplantation, year of transplant, and type of diagnosis.

All *P* values were two-sided, with values of .05 or less indicating statistical significance. For statistical analysis, we used the SAS (SAS Inc., Cary, NC) software package.

Results

The median follow-up after BMT and CBT was 70 months (range 12 to 165) and 70 months (range 12 to 151), respectively (P = NS), among surviving patients.

Graft failure; kinetics of neutrophil and platelet engraftment

Graft failure (defined as an absence of donor engraftment, autologous hematopoietic reconstitution, or receiving a second transplantation) was observed in 29/389 (7.4%) and 10/96 (10.4%) patients given BMT and CBT, respectively (P = .33). Thirty-three patients had primary graft failure, whereas 6 experienced secondary loss of the graft after transient engraftment of donor cells. The cumulative incidence of primary graft failure was 6 +/− 4% and 9 +/− 4%, in BMT and CBT, respectively (P = .77). Three of the 33 patients who had primary graft failure (1 given BMT and 2 CBT) were successfully retransplanted from the same donor 64, 46, and 48 days after the first transplant, respectively. All of these 3 patients engrafted and are alive and disease-free with a follow-up of 124, 47, and 138 months, respectively. The 2 patients who had been transplanted with CB cells had received MTX as GVHD prophylaxis in the first transplant. Six patients experienced secondary graft failure after CBT, at a median time of 151 days (range 51 to 202 days). The number of TM and SCD patients experiencing either primary or secondary graft failure after CBT was 8 and 2, respectively. Chimerism analysis in the 6 CBT recipients who had secondary graft failure showed the presence of mixed chimerism in 4 and full-donor chimerism in 2 after the initial period of hematopoietic recovery. The cumulative incidence of neutrophil recovery at day 60 was 92 +/− 1% and 90 +/− 4% in patients transplanted with BM and CB cells, respectively (P = .01). CI of neutrophil engraftment was 91% and 94% for TM and SCD, respectively (P = .31).

For patients who engrafted, the median time to neutrophil recovery after BMT and CBT was 19 days (range, 8 to 56) and 23 days (range, 9 to 60, P = .002), respectively. The median time to platelet recovery in BMT and CBT recipients was 25 days (range, 9 to 10) and 38 days (range, 13 to 125), respectively (P = .004). The CI of platelet recovery at 180 days was 85 ± 5% after BMT and 83 ± 5% after CBT. Chimerism analysis was available in 246 and 75 patients after BMT and CBT, respectively, and the proportion of long-term sustained mixed chimerism was 22% and 37% after BMT and CBT, respectively (P = .01).

Acute and chronic GVHD

Eighty-three (21%) of the 389 patients given BMT and 11 (11%) of the 96 receiving CBT experienced grade II-IV acute GVHD; no patient developed grade IV acute GVHD after CBT, as compared with 8 (2%) of those transplanted with BM cells. The CI of grade II-IV acute GVHD after BMT was 21 +/− 2%, whereas, after CBT, it was 10 +/− 3% (P = .04, see also Figure 1A).

Chronic GVHD occurred in 42 of the 355 patients at risk (ie, those surviving more than 100 days after the allograft) given BMT and in 6 of the 84 CBT recipients. Twenty-eight patients with chronic GVHD had a previous history of acute GVHD (26 had received BM and 2 CB cells). Twelve of the 42 BMT patients had extensive chronic GVHD compared with none of the CBT recipients (all the 6 CB patients developed limited chronic GVHD). The CI of chronic GVHD at 6 years in BMT recipients was 12 +/− 2%, whereas in CBT recipients, it was 5 +/− 3% (P = .12). The CI of extensive chronic GVHD at 6 years in BMT recipients was 5 +/− 9%, whereas in CBT recipients, it was 0%. A multivariate analysis for acute or chronic GVHD could not be performed because of the small number of CBT recipients developing these complications.

Transplantation-related mortality

Overall, 21 patients died of transplantation-related causes: 18 after BMT and 3 after CBT. Details on the different causes of death are

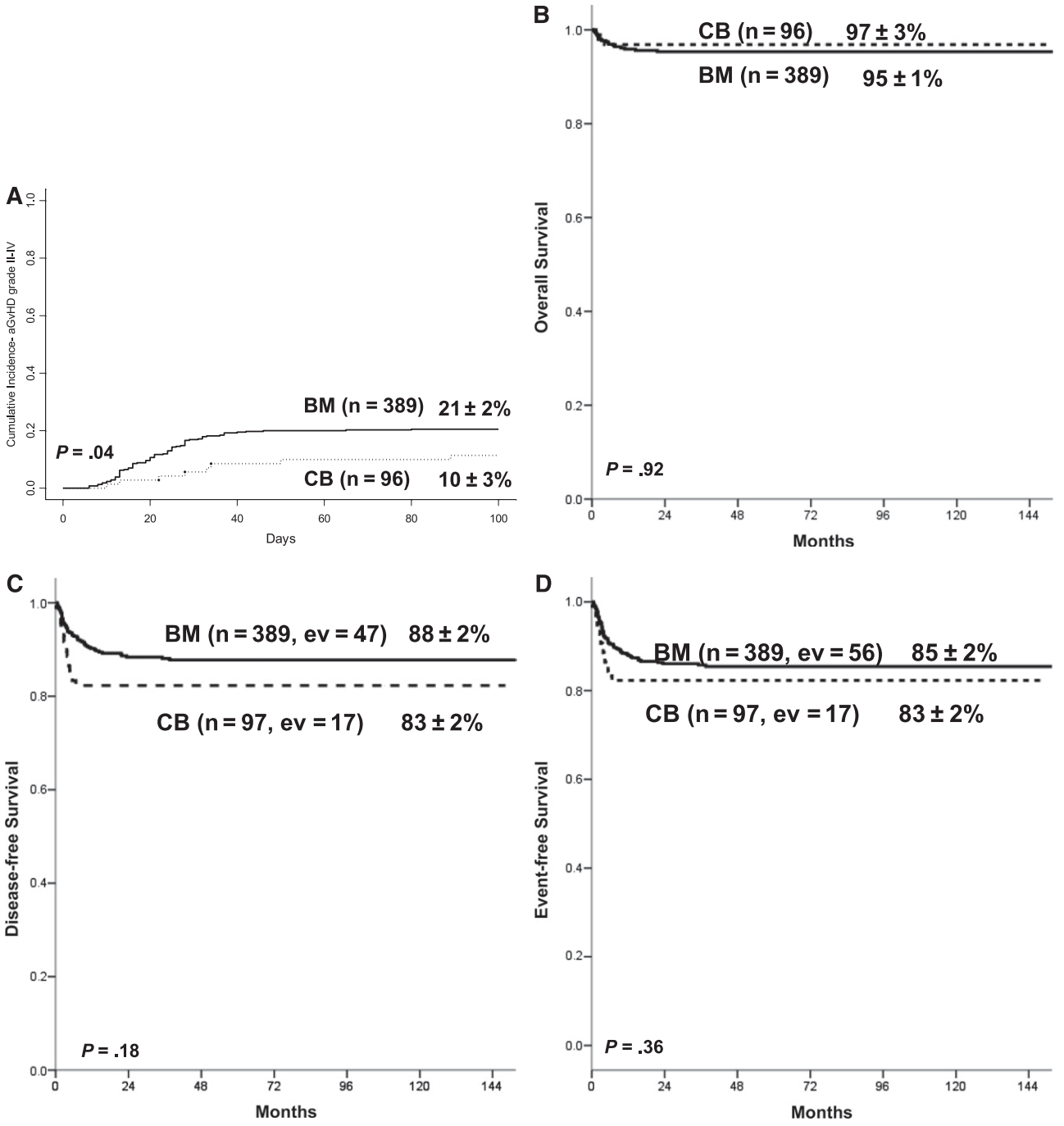

Figure 1. Cumulative incidence of grade II-IV acute GVHD and Kaplan-Meier estimates of OS, DFS and EFS. (A) Cumulative incidence of grade II-IV acute GVHD (aGVHD) for patients given BM and CB transplantation. (B) Kaplan-Meier estimate of OS for patients given BM and CB transplantation. (C) Kaplan-Meier estimate of DFS for patients given BM and CB transplantation. In the calculation of DFS, both death and graft failure were considered events. (D) Kaplan-Meier estimate of EFS for patients given BM and CB transplantation. In the calculation of EFS, death, graft failure, and extensive chronic GVHD were considered events.

shown in Table 2. GVHD was the most frequent cause of death in patients after BMT, whereas no CBT recipient died of GVHD.

Overall, disease-free, and event-free survival

A total of 371 patients are alive after BMT; 342 also survive disease-free. Of the 96 CBT recipients, 93 are alive, and 79 survive disease-free. The 6-year Kaplan-Meier estimates of OS after BMT and CBT were 95 +/− 1% and 97 +/− 2%, respectively (Figure 1B) ($P = .92$), whereas estimates of DFS after BMT and CBT were 88 +/− 2% and 83 +/− 4%, respectively (Figure 1C) ($P = .18$). To obtain a better estimation of the quality of life of surviving patients, we also calculated the 6-year Kaplan-Meier estimate of EFS (which considers also the occurrence of extensive chronic GVHD as an event): it was 85 +/− 2% and 83 +/− 2% after BMT and CBT, respectively ($P = .36$, see also Figure 1D).

A larger proportion of treatment failures occurred in patients with TM compared with those with SCD, the 6-year DFS being 84 +/− 2% and 92 +/− 2%, respectively ($P = .04$). Indeed, the

Table 2. Causes of death in the study population

	BM recipients	CB recipients	Total
GVHD	8	0	8
Hemorrhage	3	2	5
Infections	5	0	5
Organ failure	2	1	3
Total	18	3	21

6-year DFS was 86 +/− 2% and 92 +/− 2% ($P = .07$) after BMT for TM and SCD, respectively; the 6-year DFS after CBT for TM and SCD was 80 +/− 5% and 90 +/− 5% ($P = .24$), respectively. In a multivariate analysis, a diagnosis of SCD was the only variable favorably influencing the DFS probability among all the patients included in this study (hazard ratio [HR], 0.52, 95% confidence interval [CI], 0.28 to 0.97, $P = .04$).

In a subgroup analysis that focused only on the 96 CBT recipients, the outcome was significantly influenced by the use of MTX to prevent GVHD. Patients who did not or did receive MTX for GVHD prophylaxis had 6-year Kaplan-Meier DFS estimates of 90 +/− 4% and 60 +/− 11%, respectively ($P < .001$), regardless of the conditioning regimen that was administered. The use of MTX was also a significant variable in the multivariate analysis of the factors influencing DFS probability after CBT (HR 3.81, CI 1.40 to 10.87, $P = .004$). The only other variable that was associated with outcome was the period in which transplantation was performed: patients who received CBT after 1999 had a significantly better outcome (HR 0.033, CI 0.12 to 0.89, $P = .02$) compared with those treated earlier. Other factors that correlated with a better outcome after CBT included the use of TT in the conditioning regimen and, for patients with TM, belonging to class I of the Pesaro classification (data not shown). However, these variables were not significant in multivariate analysis. The number of cells infused per kg of recipient body weight influenced neither the probability of DFS nor that of sustained engraftment of donor cells (data not shown); however, it is noteworthy that most patients received a sufficient number of TNCs (median 3.9×10^7/kg, range 1.5 to 14).

Discussion

This multicenter study comparatively evaluated, after long observation, the outcome of a large population of patients with TM and SCD given either BMT or CBT from an HLA-identical sibling. Despite the limitations intrinsic to retrospective registry-based analysis, our results indicate that both CBT and BMT are equally effective in curing patients with the two most common major hemoglobinopathies, provided that an HLA-identical sibling is used as donor.

CBT from an HLA-identical sibling is widely used to treat children affected by a number of hematologic and nonhematologic conditions.[16,17,28] The previously reported advantages of CBT include a lower incidence and severity of GVHD, ease of hematopoietic stem cell procurement, negligible risk of transmission of viral infections, and no donor risk/attrition.[15,29] In this analysis, we found that the incidence of grade II-IV acute GVHD was lower in our patients transplanted with CB cells than in those receiving BMT, which confirmed previous observations,[16,28] and that grade IV acute GVHD was not recorded after CBT. Moreover, although none of the CBT recipients died of GVHD, roughly half of the fatal events after BMT were caused by GVHD. Another advantage of CBT is the complete absence of extensive chronic GVHD, which was a complication in 12 of the 355 patients at risk who had been transplanted with BM cells. Chronic GVHD can have a particularly devastating effect for patients with nonmalignant disorders,[30] who, in contrast to leukemia patients, do not benefit from the graft-versus-leukemia effect associated with the development of chronic GVHD. The quality of life of patients with extensive chronic GVHD may certainly be worse than that of TM or SCD patients treated with supportive therapy, and the risk of chronic GVHD is often considered a reason not to pursue HSCT in children who inherit these disorders. We cannot exclude that the younger age of CBT recipients could have contributed to the lower incidence and severity of GVHD in comparison with BMT recipients.

We found that both neutrophil and platelet recovery were delayed after CBT in comparison with BMT, but this feature was not associated with an increased risk of fatal infectious or hemorrhagic complications. The delayed hematological recovery observed in this cohort confirms previously published data reported in patients transplanted with CB cells from an HLA-identical sibling in comparison with BMT recipients.[16]

Occurrence of both primary and secondary graft failure remains a major limitation of HLA-identical sibling CBT in patients with TM and SCD, as it occurred in 10 of the 96 patients enrolled in this study. It occurred more frequently among TM patients. An increased risk of graft failure in CBT recipients compared with patients given BMT from an HLA-identical donor has already been reported.[16,21,28] Best results in patients given CBT can be obtained by optimizing GVHD prophylaxis and the conditioning regimen used. Indeed, our results confirm the unfavorable impact of administering MTX for GVHD prophylaxis after CBT in patients with TM or SCD.[21] In addition, the low risk of GVHD after HLA-identical sibling CBT raises concerns in general about including MTX in GVHD prophylaxis schema. As a consequence, the inclusion of MTX in GVHD prophylaxis has decreased with time.[29,31] In patients with SCD receiving either CBT or BMT from an HLA-identical sibling, the use of ATG has been reported to lower the incidence of graft failure.[9] Although we observed fewer graft failures in the cohort of CBT recipients given ATG, this favorable effect was not statistically significant (data not shown). Preparative regimens including TT, a potent myeloablative agent that can shift the balance in the competition between donor and recipient hematopoietic stem cells toward the donor, may also improve the outcome of patients with TM or SCD receiving CBT.

Although the range was rather large (see also Table 1 for details), the median number of cells infused in our CBT recipients was high (3.9×10^7/kg recipient body weight), reaching the minimal number of cells available before thawing that has been recommended by the Eurocord group (ie, at least 3.5×10^7/kg recipient body weight).[31] The achievement of this threshold was certainly facilitated by the young age of patients transplanted with CB cells. In the event that the number of nucleated cells in the CB collection is judged too few to ensure engraftment of donor cells after CBT, there is also the possibility of supplementing CB cells with BM harvested from the same sibling donor, although it has not yet been proved that this strategy will improve the recipient's outcome.

A previously published study on 27 TM recipients clearly demonstrated that sustained donor/recipient mixed chimerism of circulating leukocytes can be found in a significant proportion of patients given CBT from an HLA-identical sibling.[32] We also found that a greater proportion of CBT recipients develop sustained mixed chimerism in comparison with patients given BMT. These data suggest that CBT, more often than BMT, promotes the development of a state of reciprocal tolerance between recipient and donor cells. A threshold of the percentage of donor cells sufficient to ameliorate/resolve the symptoms of the hemoglobin disorders has

not yet been firmly established, although it has been suggested to be as low as 10% and 20% in SCD and TM, respectively.[11,33-35]

Although the use of CB cells from an HLA-identical sibling was found to be safe and largely successful in patients with hemoglobinopathies,[21] the outcome of patients given unrelated donor CBT is far less satisfactory. An unacceptably high rate of primary graft failure and TRM has been reported, resulting in a probability of DFS of only 21% and 50% for TM and SCD, respectively.[36] To explain these unsatisfactory results, it must be noted that in nonmalignant disorders, a combination of donor-recipient mismatching at HLA loci and a limited CB cell dose play a major role in engraftment, GVHD, and TRM[31,37] In view of these findings, the results of unrelated donor CBT for TM and SCD might be improved by selecting CB units that are HLA matched with the recipient and that contain a sufficient number of nucleated cells to ensure engraftment. In general, however, unrelated donor CBT in patients with TM and SCD is not recommended outside of well-designed clinical trials.

Survival rates in our patients with hemoglobinopathies who were given related CBT have improved with time. By analogy with children transplanted for hematological malignancies,[17] this might be explained by eliminating the use of MTX for GVHD prophylaxis, as well as by growing experience with CBT, resulting in better treatment of infections and other transplantation-related complications.

With the note of caution that CBT recipients were younger and transplanted in a more recent period, after adjusting for differences in multivariate analysis, this retrospective registry-based study demonstrates that CBT and BMT from an HLA-identical sibling offer comparable probability of long-term cure of the most common hemoglobinopathies. Thus, CB from an HLA identical family donor appears to be a suitable source of stem cells for HSCT of TM and SCD patients, provided that an adequate number of cells ($>3.5 \times 10^7$/kg) have been collected and cryopreserved and that MTX is not used as part of the GVHD prophylaxis. Moreover, CBT avoids discomfort caused by a marrow harvest. In view of these results, directed-donor family banking activities aimed at optimizing the cryopreservation and storage of CB of a newborn sibling should be encouraged and closely monitored to ensure that common standards are followed.[38] Future studies on the occurrence and severity of late effects after either CBT or BMT from an HLA-identical sibling are desirable for a comprehensive and meaningful comparative evaluation of these two transplant options.

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Authorship

Contribution: F.L., N.K., E.G., M.C.W., and V.R. designed the study; N.K., A.R., and V.R. prepared and analyzed data; F.L., A.R., and V.R. wrote the paper; A.G., I.R., C.K.L., F.B., C.V., J.-H.D., J.S., R.W., C.C., F.P., E.A., and G.S. provided cases for the study; and all authors edited and approved the manuscript.

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Appendix: Transplant centers that contributed cases (n = 28) (in alphabetical order by country)

Austria: Vienna - St. Anna Kinderspital
Belgium: Brussels - Cliniques Universitaires St. Luc
Bulgaria: Sofia - Children s Oncohematology Hospital
France: Créteil - Henri Mondor Hospital
France: Paris - Necker Hospital
France: Paris - Robert Debré Hospital
France: Paris - Saint-Louis Hospital
France: Rouen - Charles Nicolle-Hospital
France: Strasbourg - Hautepierre Hospital
Germany: Düsseldorf - Universitaetsklinikum
Greece: Athens - St. Sophia Children's Hospital
Hong Kong: Shatin - Prince of Wales Hospital
India: Chennai - Apollo Specialty Hospital
Iran: Tehran - Shariati Hospital
Israel: Jerusalem - Hadassah University Hospital
Israel: Petach-Tikva - Schneider Children's Medical Center of Israel
Italy: Pavia - Fondazione IRCCS Policlinico San Matteo
Italy: Rome - Roma Univ. La Sapienza
Italy: Torino - Ospedale Infantile Regina Margherita Onco-Ematologia Pediatrica
Spain: Palma De Mallorca - Hospital Universitari Son Dureta
Sweden: Lund - University Hospital
Turkey: Ankara - University Faculty of Medicine
Turkey: Ankara Cebeci - University of Ankara
United Kingdom: Manchester - Royal Manchester Children Hospital
United Kingdom: Birmingham - Birmingham Children Hospital
United Kingdom: Leeds - Mid Yorkshire Hospitals NHS Trust
United Kingdom: London - Imperial College Hammersmith Hospital
United States: Oakland - Sibling Donor Cord Blood Program

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