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Long-Term Outcomes of Cord Blood Transplantation from an HLA-Identical Sibling for Patients with Bone Marrow Failure Syndromes: A Report From Eurocord, Cord Blood Committee and Severe Aplastic Anemia Working Party of the European Society for Blood and Marrow Transplantation

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A B S T R A C T

Cord blood transplantation (CBT) from HLA-identical siblings is an attractive option for patients with bone marrow failure (BMF) syndrome because of the low risk of graft-versus-host disease (GVHD) and the absence of risk to the donor. We analyzed outcomes of 117 patients with inherited or acquired BMF syndrome who received CBT from a related HLA-identical donor in European Society for Blood and Marrow Transplantation centers between 1988 and 2014. Ninety-seven patients had inherited and 20 patients acquired BMF syndrome. Eighty-two patients received a single cord blood (CB) unit, whereas 35 patients received a combination of CB and bone marrow cells from the same donor. Median age at CBT was 6.7 years, and median follow-up was 86.7 months. The cumulative incidence function (CIF) of neutrophil recovery was 88.8% (95% CI, 83.1% to 94.9%), 100-day CIF of grades II to IV acute GVHD was 15.2%, and 7-year CIF of chronic GVHD was 14.5%. Overall survival at 7 years was 87.9% (95% CI, 80.8% to 92.6%), 89% for inherited and 81% for acquired BMF syndromes ($P = .66$). Results of this study are consistent with outcomes of bone marrow transplantation shown

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by previous series in the same setting and indicate that in pediatric patients with BMF syndrome, CBT from an HLA-identical sibling donor is associated with excellent long-term outcomes and that collection of CB unit at birth of a new sibling is strongly recommended.

INTRODUCTION

For young patients with either idiopathic or inherited bone marrow failure (BMF) syndromes, hematopoietic stem cell transplantation (HSCT) from an HLA-matched related donor represents the standard of care [1-5]. Appropriate diagnosis and accurate disease classification is imperative because both have strong implications on patient management and choice of stem cell source and preparative regimen. Also, this serves for evaluation of risk estimation (including risk of future neoplasms), genetic and medical counseling, and surveillance of patients and family members. Outcomes of BM transplantation from a related donor are excellent for acquired BMF syndromes, with overall survival (OS) approaching 90% at 3 years with a standard reduced-intensity conditioning (RIC), including cyclophosphamide (CY) and antithymoglobulin (ATG), and with cyclosporine (CSA) and methotrexate as graft-versus-host disease (GVHD) prophylaxis [2,3,6,7]. Also, the conditioning regimen combining alemtuzumab with fludarabine (FLU) and CY has been shown to reduce chronic GVHD after allogeneic HSCT for acquired aplastic anemia with good outcomes [8].

In patients with inherited BMF syndromes results have been changing over time with variable outcomes. Most studies focused on Fanconi anemia (FA), and better results have been reported in the HLA-identical related donor setting, using a low-dose CY-based regimen alone [9] or in combination with FLU [10], with survival rates over 90%. After unrelated HSCT, survival varies from 33% in previous reports [11] to 94% in more recent studies [12], with drastic improvement reported since 2000 because of better HLA typing and the use of FLU-based RIC regimens with or without T cell depletion [13,14].

HSCT using cord blood (CB) as a graft source was first performed in a patient with FA [15]. CB transplantation (CBT) from an HLA-matched related donor demonstrated the feasibility of the procedure in this category of patients; since then, CBT has been used to treat different hematologic diseases [16,17]. The Eurocord group published 2 studies [16,18] on patients receiving CBT from an HLA-identical sibling for malignant and nonmalignant hematologic diseases, which included 17 patients with BMF syndromes. In the BMF subgroup, the 1-year OS was 65% and the incidence of acute GVHD was 13% [16,18]. More recently, Bizzetto et al. [19] reported 64 patients with inherited BMF syndromes other than FA, in which 20 patients received a related and 44 an unrelated CBT. In that study, patients who underwent HLA-identical sibling CBT had better 3-year OS (95% versus 61%) and a lower incidence of acute (5% versus 11%) and chronic GVHD (24% versus 53%) than patients given unrelated CBT [19].

Currently, there are no studies reporting long-term outcomes after related HLA-identical CBT in the setting of inherited and acquired BMF syndromes. Therefore, we analyzed the outcomes of pediatric patients with BMF syndromes receiving CBT from an HLA-identical sibling.

METHODS

Data Collection

This is a retrospective, registry-based study performed by Eurocord in collaboration with the Cord Blood Committee of the Cellular Therapy and Immunobiology Working Party and the Severe Aplastic Anemia Working Party of the European Society for Blood and Marrow Transplantation (EBMT). Patients with either inherited or acquired BMF syndromes (diagnosed according to standard criteria) [20,21] and receiving a CBT from an HLA-identical sibling, alone or in combination with other stem cell sources from the same donor, from 1988 to 2014 were included in the study. Demographic and clinical data were extracted from the Eurocord database and validated. A specific questionnaire was sent to all participating centers to collect data on pretransplant treatments and long-term outcomes. All data were verified and updated by the transplant center physicians and data managers.

Parents or legal guardians provided informed consent allowing data entry into the Eurocord and EBMT databases for research purposes. The study was conducted in compliance with the Declaration of Helsinki. The Internal Review Board of Eurocord/EBMT reviewed and approved the study.

Endpoint Definitions

The primary endpoint was OS, defined as time from transplantation to death of any cause. Other endpoints included neutrophil recovery and graft failure, acute and chronic GVHD, overall mortality, event-free survival (EFS) and GVHD-free survival (GFS). EFS was calculated from the date of transplantation to the first event, with death and graft failure considered as events. GFS was calculated from the date of transplantation to the first event, with death and acute GVHD grade ≥ III and/or extensive chronic GVHD considered as events.

Neutrophil recovery was defined as the first of 3 consecutive days with a neutrophil count $\geq .5 \times 10^9$/L. Graft failure was defined as neutrophil count never reaching $.5 \times 10^9$/L, evidence of autologous reconstitution, or neutrophil count reaching $.5 \times 10^9$/L, with subsequent, nontransitory decrease in neutrophil count or loss of donor chimerism. The evaluation of early graft failure was based on chimerism evidence within the first 100 days post-transplant. Acute and chronic GVHD were diagnosed and graded according to published criteria [22,23].

Myeloablative conditioning (MAC) was defined as a regimen containing total body irradiation with a dose > 6 gray or busulfan at dose > 8 mg/kg oral or >6.4 mg/kg i.v. A supplementary analysis of long-term complications was performed for patients with available updated information.

Statistical Analysis

Probabilities of survival for OS, EFS, and GFS were calculated using Kaplan-Meier estimates and compared with the log-rank test. In the case of nonevent, observations were censored at the time of last follow-up. Cumulative incidence function (CIF) was used in a competing risk setting, with death from any cause treated as a competing event to calculate engraftment and acute and chronic GVHD using Gray's test [24]. Statistical analyses were performed with SPSS 22 (SPSS Inc., Chicago, IL) and R-Project 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria) software packages. Multivariate analysis was not performed because of the low number of events reported.

RESULTS

Patient, Disease, and Transplant Characteristics

A total of 117 patients from 62 EBMT transplant centers were analyzed. Patient, disease, and transplantation characteristics are summarized in Table 1. Briefly, 97 patients had inherited BMF syndromes (48 patients were diagnosed with FA, 2 patients with Schwachman-Diamond syndrome [SDS], 3 patients with dyskeratosis congenita [DC], 5 with amegakaryocytic thrombocytopenia, 27 with Diamond-Blackfan anemia [DBA], 4 with Kostmann syndrome/congenital neutropenia [KS/CN], and 8 with other inherited syndrome] and 20 patients acquired BMF syndromes (19 patients diagnosed with aplastic anemia [AA] and 1 patient with pure red cell aplasia).

Median age at CBT was 6.7 years (range, 1 to 16), and median interval from diagnosis to CBT was 49.8 months (range, 2 to 160). Median follow-up after CBT was 86.7 months (range, 1.5 to 325) (Table 1). Information on transfusion before

Table 1
Patient, Disease, and Transplantation Characteristics

	Acquired (n = 20)	Inherited (n = 97)	Overall (N = 117)
Median follow-up, mo (range)	119.1 (1.5-293.4)	83.9 (2.9-325.2)	86.7 (1.5-325.2)
Median age at diagnosis, yr (range)	4.05 (1-11.3)	.9 (0-8.6)	1.5 (0-11.3)
Median age at transplantation, yr (range)	5.6 (2.5-14.5)	6.9 (1.2-16.4)	6.7 (1.2-16.4)
Weight at transplantation, kg	22.6 (11.7-50.3)	19.9 (9.0-68.0)	20.0 (9.0-68.0)
More than 20 RBC units infused	9/12 (75)	35/71 (49)	44/83 (53)
More than 20 platelet transfusions	10/12 (83)	13/71 (18)	23/83 (28)
Previous therapy for BMF	12/15 (80)	46/74 (62)	58/89 (65)
Previous ATG	10/14 (71)	4/72 (6)	14/86 (16)
Previous steroids	10/14 (71)	32/73 (44)	42/87 (48)
Previous androgens	0/10 (0)	11/37 (30)	11/47 (23)
Previous CSA	11/15 (73)	2/73 (3)	13/88 (15)
Previous GF	6/14 (43)	12/73 (16)	18/87 (21)
Median interval between diagnosis and CBT, mo (range)	18.5 (3.9-106.6)	54.9 (2.1-159.8)	49.8 (2.1-159.8)
CMV status			
Recipient positive	11/18(61)	50/94 (53)	61/112 (55)
Recipient negative	7/18 (39)	44/94 (47)	51/112 (46)
Stem cell source			
CB alone	13/20 (65)	69/97 (71)	82/117 (70)
CB+BM	7/20 (35)	28/97 (29)	35/117 (30)
Conditioning regimen			
RIC	16/20 (80)	52/91 (57)	68/111(61)
MAC	4/20 (20)	39/91 (43)	43/111 (39)
Use of TBI	1/20 (95)	4/96 (4)	5/116 (64)
Use of Fludarabine	6/19 (32)	53/93 (57)	59/112 (53)
Use of ATG	8/19 (42)	53/97 (56)	61/113 (54)

Because some data were not available for the entire cohort, values are n/N with percents in parentheses, unless otherwise noted. GF indicates growth-factor; TBI, total body irradiation.

CBT was available for 83 patients; 44 of them (53%) received > 20 units RBCs and 23 (28%) received > 20 platelets units.

From patients with available information (n = 89), 65% received treatment for BMF syndromes before CBT. For patients with acquired BMF, 3 did not receive any treatment before CBT, 10 patients received at least 1 course of ATG in association with CSA ± steroids ± growth factors, and 1 patient had steroids + CSA. Among patients with inherited BMF syndromes, 32 were treated with steroids (of these, 4 also received ATG), 12 with growth factors, and 11 with androgens, whereas CSA was used in 2 patients and 2 patients received substitutive prophylaxis with immunoglobulin.

Eighty-two patients received a single CB unit, whereas 35 received CB in combination with BM (CB+BM) from the same donor. At cryopreservation, the median number of total nucleated cells (TNCs) and $CD34^+$ was 5.6×10^7/kg (range, 1.04 to 24.28) and 1.4×10^5/kg (range, .13 to 9.09), respectively, for patients who received single CBT. The median infused TNC was 4.7×10^7/kg (range, .83 to 18.85) and median number of $CD34^+$ cells 1.2×10^5/kg (range, .1 to 24.4) for single CBT patients. For the 35 patients receiving a combination of CB+BM, the graft composition consisted of a median TNC at cryopreservation of 3.5×10^7/kg (range, .63 to 8.43) for CB and 22.3×10^7/kg (range, 3.8 to 39.0) for BM.

Conditioning regimen varied according to the type of BMF syndrome and transplant center policy. Sixty-eight patients (61%; 16 patients with acquired and 52 with inherited BMF) received a RIC and 43 patients (39%; 4 with acquired and 39 with inherited BMF syndromes) a MAC (missing data for 6 patients).

FLU-based regimens were used in 59 patients (53%). The most common chemotherapy associations were CY and FLU (n = 37, 54%) in the RIC setting and CY and busulfan (n = 30, 70%) for patients receiving a MAC. Total body irradiation was used in 5 patients: 2 received >6 Gy (1 patient had severe AA and 1 FA) and 3 received <6 Gy (1 FA, 1 DBA, and 1 DC). ATG as part of the conditioning regimen was used before CBT in 8 patients (42%) with acquired and in 53 patients (56%) with inherited BMF syndromes, respectively (45% in MAC and 61% in RIC setting). GVHD prophylaxis consisted, mainly, of CSA alone or with steroids in 70 patients (60%) and CSA + methotrexate in 20 patients (17%); CSA + mycophenolate mofetil was used in 11 cases (9%).

Engraftment and GVHD

CIF of neutrophil recovery at day 60 was 84.2% (95% confidence interval [CI], 67.8% to 100%) in acquired and 89.7% (95% CI, 83.7% to 96.1%) in inherited BMF syndromes, respectively, ($P = .13$, Table 2), with a median time to engraftment of 21 days (range, 7 to 105) (median of 26 days for acquired and 18 for inherited BMF syndromes). Chimerism analysis was available in 69 of 117 patients: 53 patients (68%) had full donor chimerism, 12 (15%) mixed chimerism, and 4 (5%) autologous reconstitution (all in patients with inherited BMF syndromes [1 DBA, 1 KS/CN, and 2 other]). Twelve patients failed to achieve neutrophil engraftment (11 patients after receiving a single CB unit and 1 after a CB+BM graft). Of the patients who failed to engraft, 2 had acquired and 10 had inherited BMF syndromes (4 with FA, 1 with DC, 1 with KS/CN, 1 DBA, and 3 other). For those with available information, treatment of primary graft failure was a second HSCT in 7 patients, with a BM graft in 5 patients (2 from the same donor and 3 from an unrelated donor) and CB in 1 patient. Among the 12 patients with primary graft failure, 3 were alive at last follow-up after rescue with the second HSCT and 9 died at a median of 1.4 months (range, .1 to 6.3) after the first CBT. Results of the univariate analysis are reported in Table 2. The use of FLU in the conditioning regimen was associated with a higher incidence of engraftment (91% versus 85%, $P = .01$).

Table 2
Univariate Analysis

Variables	7-Year OS			7-Year EFS			CIF of Neutrophil Engraftment			CIF of Acute GVHD			CIF of Chronic GVHD		
	% at 7 Yr	95% CI	*P*	% at 7 Yr	95% CI	*P*	% at 60 Days	95% CI	*P*	% at 100 Days	95% CI	*P*	% at 7 Yr	95% CI	*P*
All patients	87.9	80.8-92.6		85.3	75.8-91.5		88.8	83.1-94.9		15.2	9.8-23.6		14.5	8.6-24.2	
Patient gender															
Male	93.3	84.9-97.2	.033	91.9	80.5-96.9	.210	93.7	87.4-100	.298	12.9	6.7-24.8	.417	9.9	4.3-23.2	.291
Female	81.3	67.1-90.2		77.3	63.8-86.8		82.7	72.6-94.1		18.4	10.1-33.4		20.2	10.6-38.4	
Year of CBT															
≤2007	86.5	76.8-92.5	.555	82.1	70.4-89.8	.213	83.8	75.3-93.3	.008	15.2	8.5-26.9	.987	17.1	9.6-30.2	.288
>2007	91.3	80.2-96.4		91.2	76.5-97.1		95.8	89.5-102.6		15.2	7.6-30.3		10.6	3.4-33.1	
Age at transplant															
<6.7 yr	89.5	79.1-95.0	.851	86.0	73.5-93.1	.920	87.9	79.6-97.1	.612	16.1	8.8-29.4	.573	14.3	6.6-30.9	.870
≥6.7 yr	85.9	73.5-93.1		84.2	72.2-91.6		89.3	81.2-98.2		13.0	6.4-26.1		15.0	7.5-30.0	
Weight at transplant															
<20 kg	93.6	81.0-98.0	.294	87.2	74.4-94.1	.928	87.2	77.7-97.9	.942	15.6	7.8-31	.890	22.5	12.5-40.8	.037
≥20 kg	83.6	68.9-92.1		83.6	68.9-92.1		89.1	80.0-99.4		17.4	9.2-32.9		7.1	2.3-21.4	
CMV patient status															
Negative	88.9	75.5-95.4	.498	84.9	72.7-92.2	.769	94.0	87.1-100	.053	20.0	11.4-35	.154	16.2	8.1-32.4	.642
Positive	88.1	78.1-93.9		86.9	77.1-92.9		85.2	76.5-95.0		10.5	4.9-22.6		10.5	4.5-24.4	
Type of BMF															
Acquired	81.3	56.4-93.6	.669	81.1	56.3-93.5	.931	84.2	67.8-100.0	.131	5.6	.8-39.4	.236	7.8	1.1-55.5	.188
Inherited	89.4	82.1-94.0		86.4	76.7-92.4		89.7	83.7-96.1		17	10.9-26.7		15.3	9.0-26.0	
Subtype of BMF															
Acquired	81.3	56.4-93.6	.225	81.1	56.3-93.5	.069	84.2	67.8-100.0	.053	5.6	.8-39.4	.026	7.8	1.1-55.5	.129
FA	89.4	75.8-95.8		89.4	75.8-95.8		91.7	83.5-100.0		17	9-32.2		22.2	11.7-41.9	
DBA	96.3	79.5-99.4		92.6	76.8-97.9		96.3	87.5-100.0		29.6	16.4-53.7		12.5	4.2-36.9	
Other inherited	81.3	61.8-92.1		72.2	50.3-86.9		77.3	60.7-98.3		0	N/A		5.6	.8-39.6	
Time from diagnosis to CBT															
<48 mo	87.5	77.6-93.4	.595	85.8	73.4-93.0	.781	86.0	77.1-95.9	.567	10.9	5.1-23.4	.241	11,6	5-27.3	.389
≥48 mo	88.0	74.9-94.7		84.5	72.4-91.9		91.4	84-99.4		19.3	11.3-33		16,8	8.9-32.0	
Conditioning regimen															
MAC	88.4	75.2-95.0	.717	83.7	69.0-92.2	.425	86.0	75.8-97.6	.425	17.1	8.6-33.8	.324	11,2	4.4-28.6	.616
RIC	87.7	74.7-94.5		86.1	73.6-93.2		89.6	82.2-97.5		10.8	5.3-21.8		14,5	7.1-29.7	
FLU based															
No	84.5	72.4-91.5	.191	82.7	70.9-90.4	.315	84.9	75.5-95.5	.011	13.5	6.7-27	.948	15.2	7.6-30.4	.837
Yes	92.9	80.9-97.6		89.4	79.0-95.0		91.5	84.3-99.4		14.3	7.5-27.3		14.0	6.5-30	
ATG use															
No	87.3	74;5-94.2	.866	87.3	74.5-94.2	.596	90.4	82.2-99.3	.912	18.0	9.9-32.7	.335	12.8	6.0-27.2	.933
Yes	87.8	77.9-93.6		83.0	71.2-90.6		86.9	78.5-96.1		11.9	5.9-23.9		16.9	8.4-33.9	

At day 100, CIF of grades II to IV acute GVHD was 17% (95% CI, 10.9% to 26.7%) for inherited and 5.6% (95% CI, .8% to 39.4%) for acquired BMF syndromes ($P = .23$) (Table 2). Overall, 17 patients experienced grades II to IV acute GVHD (11 grade II, 5 grade III, and 1 grade IV). The CIF of chronic GVHD at 7 years was 14.5% (95% CI, 8.6% to 24.2%), 15.3% (95% CI, 9% to 26%) for inherited and 7.8% (95% CI, 1.1% to 55.5%) for acquired BMF syndromes ($P = .18$). Sixteen patients experienced chronic GVHD (limited, 8; extensive, 7; 1 missing grade).

Overall Mortality, OS, EFS, and GFS

Overall mortality at 1 year was 10.6% (95% CI, 6.0% to 17.9%), with no difference according to the type of diagnosis ($P = .66$). Overall, 14 patients died, 9 experiencing primary graft failure and 5 fully engrafted (3 patients with acquired and 11 with inherited BMF syndromes, among whom 5 patients had FA). Causes of death were infections in 6 patients, GVHD (after a second HSCT for primary graft failure) in 1 patient, acute respiratory distress syndrome in 1 patient, hemorrhagic syndrome in 1 patient, and other causes in the remaining 5 patients.

Probability of 7-year OS was 87.9% (95% CI, 80.8% to 92.6%) with no difference between the acquired and inherited group (81.3% [95% CI, 56.4% to 93.6%] and 89.4% [95% CI, 82.1% to 94.0%], respectively; $P = .67$) (Table 2, Figure 1). According to stem cell source, 7-year OS was 86.1% (95% CI 76.5% to 92.2%) for patients receiving CB alone and 91.3% (95% CI, 72.7% to 97.6%) for those receiving CB+BM ($P = .18$) (Table 2).

The 7 year-EFS was 85.3% (95% CI, 75.8% to 91.5%), with no difference according to the type of BMF syndrome (81.1% [95% CI, 56.3% to 93.5%] for acquired and 86.4% [95% CI, 76.7% to 92.4%] for inherited; $P = .93$) (Table 2, Figure 2) and according to the type of stem cell source used (83.7% [95% CI, 74.4% to 90.1%] for CB alone and 88.7% [95% CI, 68.6% to 96.6%] for CB+BM, $P = .23$) (Table 2). GFS at 7 years was 78.4% (95% CI, 69.5% to 85.2%): 81.1% (95% CI, 56.3% to 93.5%) for patients with acquired and 78.1% (95% CI, 69.4% to 84.9%) for those with inherited BMF syndromes ($P = .34$). For patients who received CB alone, the 7-year GFS was 77.7% (95% CI, 66.6% to 85.9%) versus 79.3% (95% CI, 60.4% to 90.6%) for patients who received a combined CB+BM ($P = .41$).

Long-Term Results

Information on long-term outcomes was available for 87 of 117 patients (Table 3). Overall, at least 1 type of organ dysfunction was reported in 23 patients. Endocrine dysfunction (hypothyroidism, osteoporosis, growth retardation, hypogonadism, and/or sexual impairment) was the most common impairment reported, being described in 14 of 87 cases. A pregnancy 19 years after CBT was reported for 1 patient transplanted for severe AA at the age of 10 and receiving CY and ATG as conditioning regimen. One patient diagnosed with DC experienced bilateral cataracts 26 months after CBT.

Two patients, both diagnosed with FA, had oral mucosal damage. One of them, who also had chronic GVHD, developed nonmalignant leukoplakia, diagnosed 1 year after CBT. Cardiovascular disorders were reported in 2 patients with FA; of them, 1 was diagnosed with left ventricular hypertrophy and the other developed chronic heart failure (he had a history of congenital aortis coartation before CBT). Esophagitis was reported in a patient with DBA.

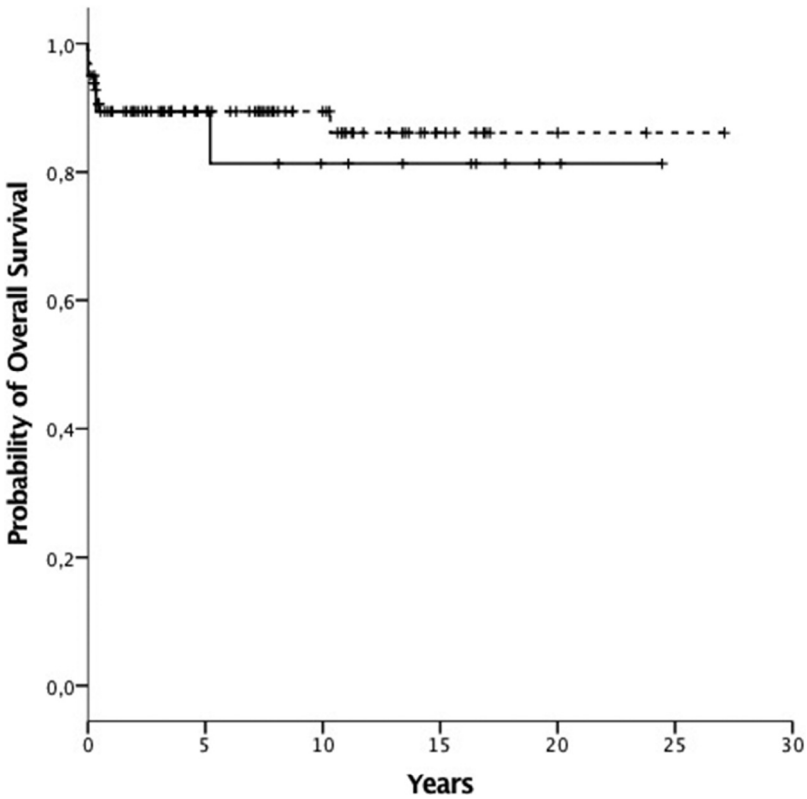

Figure 1. OS for patients with inherited (*dotted line*) and acquired (*solid line*) BMF syndromes ($P = .669$).

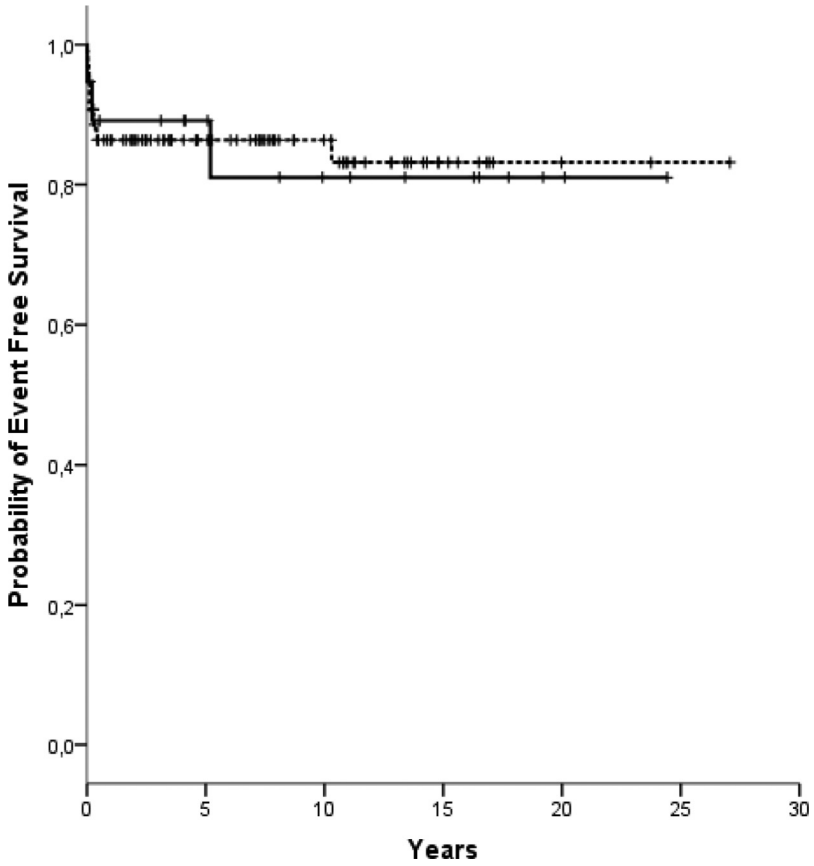

Figure 2. EFS for patients with inherited (*dotted line*) and acquired (*solid line*) BMF syndromes ($P = .931$).

One patient, diagnosed with DBA, developed nonmetastatic osteosarcoma 9 years after CBT. The patient did not have a history of chronic GVHD or post-transplantation complications, the immunosuppressive therapy having been discontinued 1 year after CBT. The secondary malignancy was treated with a combined neoadjuvant and surgical treatment in the setting of a phase II trial (NCT01459484), allowing a partial response. The patient had a partial response to the treatment and was alive with neoplasia at the last follow-up. Other types of dysfunctions were reported in 10 patients and included iron overload (reported in 1 patient with acquired BMF syndrome, heavily transfused before CBT), attention deficit (reported in 2 patients, 1 with FA and 1 with DBA), pseudo-arthrosis, and avascular necrosis (both reported in 2 patients with FA).

DISCUSSION

In this study we report the outcomes of 117 patients with BMF syndromes who underwent CBT from an HLA-identical donor over a 28-year period; this represents the largest series reporting outcomes in this setting. CB is an attractive source, particularly for nonmalignant diseases, because of the reduced risk of GVHD for the recipient and the absence of medical risk for the donor. Family CB collection programs have been established given the excellent results observed not only in BMF syndromes but also in other hereditary disorders, such as hemoglobinopathies, metabolic disorders, and congenital immune deficiencies [25-27]. Nevertheless, it is important to emphasize that in the setting of inherited BMF syndromes, it is necessary to perform genetic tests in the stored related CB unit or donor.

In this series most patients received CB alone and 35 received a graft composed of CB and BM from the same donor. The main reason for the combined CB+BM graft was the low TNC dose of the single CB unit available. The TNC dose is one of the most important factors associated with CBT outcomes in both the related and unrelated setting [28]. For patients with nonmalignant diseases the risk of graft failure is high and should be avoided. It has been previously shown that the addition of BM from the same donor to CB units with low TNC dose may reduce the risk of nonengraftment and improve survival [29]; however, we were unable to detect any difference in survival, probably because of the low number of events. Nonetheless, neutrophil engraftment was higher for the CB+BM group.

Rocha et al. [30] compared the outcomes of pediatric patients receiving BM transplantation and CBT from HLA-identical siblings and showed that incidences of acute and chronic GVHD were lower in the CBT group, which is in agreement with results reported in other studies in the BMF settings [31-33]. Results of CBT in our analysis are similar to those of BM transplantation from HLA-identical sibling donors in the acquired BMF setting. OS for patients with severe AA ranges from 85% to 90% for patients younger than 20 years [34,35]. Concerning inherited BMF syndromes, Shimada et al. [36] reported excellent outcomes of BM transplantation in a limited cohort of 8 FA pediatric patients (OS reaching 100% for a median post-transplant follow-up of 72 months)

Table 3
Long-Term Complications*

Diagnosis	Age at CBT (yr)	Conditioning Regimen	Conditioning Intensity	Grades II-IV Acute GVHD	Chronic GVHD	Type of Impairment	Survival	Follow-up (mo)
FA	5.7	CY+FLU	RIC	No	No	Growth disturbance, other impairment	Alive	36.2
FA	5.7	CY	RIC	No	Extensive	Hypogonadism, attention deficit	Alive	325.2
AA	12.4	CY + TBI	MAC	No	No	Endocrinologic impairment, osteopenia, iron overload	Alive	241.6
FA	4.7	CY	RIC	No	Limited	Left ventricular hypertrophy	Alive	202.2
FA	1.2	CY+FLU	RIC	No	No	Chronic heart problems (known congenital coarctation aortis)	Alive	104.7
AA	10.0	CY / ATG	RIC	No	No	Endocrinologic impairment, other impairment	Alive	230.7
AA	5.1	CY / ATG	RIC	No	Limited	Endocrinologic impairment, other impairment	Alive	195.7
FA	6.7	CY+Bu	RIC	No	No	Endocrinologic impairment	Alive	182.8
DBA	4.6	CY+Bu	MAC	No	No	Attention deficit, other impairment	Alive	171.9
FA	11.8	CY+FLU / ATG	RIC	Grade II	No	Avascular necrosis of hip	Alive	95.1
FA	6.9	CY+FLU / ATG	RIC	No	No	Endocrinologic impairment	Alive	129.7
FA	7.6	CY+FLU / ATG	RIC	No	no	Nonmalignant leukoplakia	Alive	123.5
DBA	4.8	CY+Bu / ATG	MAC	No	Limited	Esophagitis, endocrinologic impairment, pseudoarthrose	Alive	163.9
DBA	6.7	CY+Bu / ATG	MAC	Grade II	No	Endocrinologic impairment	Alive	72.6
FA	3.7	CY+FLU	RIC	No	No	Endocrinologic impairment	Alive	154.0
FA	10.1	CY+FLU	RIC	Grade II	Limited	Other impairment	Alive	162.0
DBA	10.0	Bu+FLU+Thio	MAC	No	No	Osteosarcoma	Alive	160.6
DBA	12.5	CY+Bu	MAC	No	Extensive	Hypogonadism, hypothyroidism	Alive	104.4
FA	10	CY+TBI / ATG	RIC	No	No	Endocrinologic impairment	Alive	205.4
FA	10.5	CY+FLU / ATG	RIC	No	No	Endocrinologic impairment	Alive	140.7
FA	16.4	CY+FLU / ATG	RIC	No	Extensive	Oral mucosal damage	Alive	41.3
DC	6.3	CY+FLU+TBI / ATG	RIC	no	No	Ophthalmologic impairment	Alive	38.6
KS/CN	7.9	FLU+Thio+Melph / ATG	RIC	no	No	Other impairments	Alive	55.2

Bu indicates Busulphan; Thio, Thiotepa; Mel, Melphalan.
* Data available for 87 patients.

receiving FLU/low-dose CY/ATG-based conditioning regimen. The EBMT published a survey of 795 FA patients undergoing HSCT. In this series, 471 FA patients were transplanted with an HLA-identical sibling graft and OS reached 80% at 5 years [37].

In our study, CBT was associated with a low incidence of acute and chronic GVHD. The ATG use in our population might have contributed to this result. In addition, the low number of $CD3^+$ cells in CB units may also have played a role in decreasing the incidence of GVHD. It is important to point out that reducing the risk of GVHD is extremely important in the setting of nonmalignant diseases such as BMF, because nonmalignant diseases do not benefit of the "graft-versus-disease" effect in the control of relapse [38].

Given the long period covered in this study, the conditioning regimens and GVHD prophylaxis protocols were heterogeneous. In our study we did not observe a difference in survival between MAC and RIC recipients. We restrain from making any general recommendations regarding the conditioning intensity in the BMF setting because it varies according to the specific disease. Conditioning regimen and GVHD prophylaxis for BM transplantation from a related donor for patients with idiopathic AA are well established, using standard doses of CY with ATG and CSA and methotrexate [2]. However, in inherited BMF syndromes (most data derived from studies on FA), high doses of CY or use of busulfan have been associated with a high transplantation-related mortality and prohibitive incidence of acute and chronic GVHD [37].

FA cells are characterized by hypersensitivity to alkylating agents in vitro [39] and radiation in vivo [40]. Over the past 3 decades modifications of conditioning regimen together with advances in transplant medicine have dramatically improved the outcomes of allogeneic HSCT for FA [37]. Reduction of doses of chemotherapy and radiation [41], incorporation of FLU into preparative regimens [42], and in vivo and/or ex vivo T cell depletion of the graft [43] were able to decrease toxicity and incidence and severity of GVHD and to enhance engraftment [13,14,37,44].

FLU is now part of the standard preparative regimen for FA patients also in the unrelated CBT setting [45]. In our study the use of FLU was associated with better engraftment. The impact of year of transplant observed in the neutrophil engraftment may be due to change in conditioning regimen practices over the years, including the increased use of FLU.

Importantly, we were able to analyze a subset of patients with long-term follow-up (87/117 patients). Importantly, only 1 child, diagnosed with DBA, developed a second solid tumor. Giving the natural history of most inherited BMF syndromes, in particularly osteosarcoma in DBA [46], characterized to be associated with an increased risk of malignancies [47,48], this event could be likely related to the disease per se and not to the toxicity of the transplant procedure. Nevertheless, it is noteworthy that a longer follow-up of the BMF cohort (10 to 15 years) would have been necessary to have a better appreciation of the incidence of secondary malignancy in the studied population.

One pregnancy was reported 19 years after CBT in a patient transplanted for severe AA. The reported overall conception rate after HSCT is low; however, it may vary according to the underlying disease and conditioning regimen intensity [49]. In a previous series on 43 patients transplanted for AA after CY 200 mg/kg, 9 experienced pregnancy (total of 12 pregnancies), resulting in 8 live births [50]. In the setting of inherited BMF syndromes, 10 pregnancies were reported in a series of 101 FA patients aged 16 years or older [51]. Nonetheless, scarce information is available in the literature about fertility, pregnancy, and childbirth after CBT; therefore, comprehensive and multidisciplinary follow-up is important to monitor fertility status.

It is important to note that only long-term organ impairments and dysfunctions that were explicitly reported by the participating transplant centers (40/62 participating centers provided data on long-term outcomes) are described in this report; therefore, the actual number of patients experiencing long-term organ involvement may be under-represented. This is a common weakness of retrospective registry–based studies such as ours. Nevertheless, even if the information on late outcomes presented in our article is not exhaustive, it remains of interest to the current literature because of the rarity of the disease reported in our cohort and long follow-up describing major transplant outcomes.

The retrospective nature of the study, the heterogeneity of conditioning regimen and supportive care, and changes in CBT procedures during the study period are drawbacks of this study. Despite these limitations, we believe that our results may be useful for BMF research and management, especially for patients with inherited BMF syndromes.

In conclusion, in children and adolescents with BMF syndromes, CBT from an HLA-identical sibling is associated with excellent outcomes, with an OS around 90% at 7 years and low incidence of acute and chronic GVHD. Therefore, CBT from an HLA-identical sibling is a valid option in children with BMF syndromes. CB collection at the birth of a new sibling should be recommended, especially in case of inherited BMF syndromes. The combination of CB with BM stem cells might impact long-term outcomes by improving initial engraftment and, possibly, by improving immune recovery through the adoptive transfer of antigen-experienced T cells to the recipient. Comprehensive follow-up with a multidisciplinary team is necessary in patients undergoing HSCT for BMF to detect long-term complications and to evaluate reintegration to school and quality of life.

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