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Brief Articles

Unrelated Cord Blood Transplantation for Patients with Primary or Secondary Myelofibrosis

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A B S T R A C T

To determine whether umbilical cord blood transplantation (UCBT) is an alternative cure for myelofibrosis (MF), we evaluated 35 UCBTs reported to Eurocord. Seven patients had secondary acute myeloid leukemia (AML) at UCBT, and median age at UCBT was 54 years. Twenty-four patients received a reduced-intensity conditioning (RIC) regimen, and 17 of 35 patients received total body irradiation (2 to 12 Gy)-fludarabine-cyclophosphamide (TCF) conditioning. The median follow-up was 24 months. The cumulative incidence of neutrophil recovery at 60 days was 80%. Fifteen patients relapsed after UCBT. The 2-year overall survival and event-free-survival (EFS) rates were 44% and 30%, respectively. All patients given TCF achieved neutrophil and platelet recovery, and the use of TCF was associated with superior EFS in the RIC population (44% versus 0%,

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$P = .001$). Patients with transformation to AML had similar outcomes to patients with less advanced stages. In conclusion, despite graft failure remaining a major concern, the role of UCBT in the management of MF, especially using RIC TCF-based regimens, deserves further investigation to improve results.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) is currently the only curative option for patients with primary myelofibrosis (PMF) and myelofibrosis secondary to polycythemia vera or essential thrombocythemia (SMF). Several studies have shown survival rates of 40% to 60% after HSCT [1–5]. Transplant-related mortality (TRM) remains relatively high (10% to 40%) pursuant to inherent features of the underlying disease, such as its presentation commonly at an advanced age. HSCT is therefore usually reserved for the minority of younger higher risk patients [1–5].

The use of reduced-intensity conditioning (RIC) in patients with myelofibrosis (MF) has been explored, showing its applicability in older patients [6–9]. Umbilical cord blood transplantation (UCBT) is a valid alternative for patients lacking an HLA-matched donor [10,11] and double UCBT has extended this procedure to adults [12]. In a previous report, Takagi et al. [13] showed engraftment in 13 patients and a 4-year overall survival (OS) of 28% after RIC UCBT in 14 patients with hematological malignancies associated with bone marrow fibrosis, including 1 case of PMF and 1 of SMF. Another recent study compared outcomes of unrelated UCBT with other related and unrelated hematopoietic stem cell sources in patients with PMF given myeloablative (MAC) or nonmyeloablative conditioning. Lower neutrophil engraftment and higher TRM were reported after UCBT. The type of stem cell source did not appear to have an impact on OS (36% at 2 years), although the small number of UCBTs (N = 11) did not allow for definitive conclusions in this trial [14]. In this retrospective registry-based analysis, we describe UCBT outcomes in a series of patients with PMF or SMF.

METHODS

Data were retrieved from the Eurocord database and supplemented using the EBMT registry; a questionnaire was sent to the centers to complete missing data and to confirm the diagnosis. Neutrophil recovery was defined as an absolute neutrophil count $\geq .5 \times 10^9$/L for 3 consecutive days and platelet recovery as a platelet count $\geq 20 \times 10^9$/L for 7 consecutive days without transfusion support. Graft failure (GF) was defined as never having reached neutrophils $\geq .5 \times 10^9$/L within the first 60 days after UCBT or documentation of autologous reconstitution by chimerism analysis. MAC was defined as a regimen containing either total body irradiation (TBI) with a dose $\geq$6 Gy, a dose of oral busulfan >8 mg/kg or, a dose of intravenous busulfan >6.4 mg/kg.

The Kaplan-Meier method was used to estimate OS and event free survival (EFS), considering GF, relapse, and death as events. Cumulative incidence was performed to estimate neutrophil and platelet recovery, relapse, and TRM. Considering the small number of patients, multivariate analysis was not performed. Statistical analysis was processed on SPSS version 19 (SPSS Inc., Chicago, IL) and S-Plus (MathSoft) software packages (Insightful Corp., Seattle, WA).

All patients provided informed consent for data treatment, according to the Declaration of Helsinki. This study was approved by the International Review Board of Eurocord and CMWP-EBMT.

Thirty-five patients with PMF (n = 20) or SMF (n = 15) who underwent a double (n = 22) or single (n = 13) UCBT between 2005 and 2012 in 23 EBMT centers were reported to Eurocord. Seven cases (3 PMF and 4 SMF) had transformed into acute myeloid leukemia (AML) at the time of UCBT: 4 were transplanted in complete remission. Patient, disease, and transplant characteristics are shown in Table 1.

The median age at UCBT was 54 years (range, 28 to 63). The median time from diagnosis of MF to UCBT was 27 months for PMF (range, 5 to 150) and 10 months for SMF (range, 1.4 to 111). The median time from AML diagnosis to UCBT was 6 months (range, .1 to 99). Fifteen patients (43%) underwent splenectomy before UCBT, and the median time from splenectomy to transplantation was 8 months (range, 2 to 206). Eleven patients (31%) received a MAC regimen and 24 (69%) a RIC. The most common conditioning regimen was TBI associated with cyclophosphamide and fludarabine (TCF, n = 17): of these, 4 patients received TCF with a myeloablative TBI dose of 12 Gy and 13 had a RIC with low-dose TBI 2 Gy. Cord blood units were 5/6 and 4/6 HLA matched to the recipient in 23% and 77% of the cases, respectively. Graft-versus-host disease (GVHD) prophylaxis was calcineurin inhibitor based for 34 patients (97%), given with mycophenolate mofetil in 19 of those patients (54%).

RESULTS

Hematological Recovery

Neutrophil recovery was achieved in 28 patients at a median time of 30 days (range, 11 to 60), whereas 19 had platelet recovery at a median time of 42 days (range, 13 to 91). Cumulative incidences of day 60 neutrophil recovery and day 100 platelet recovery were 80% (Figure 1A) and 54%, respectively. Among patients who achieved neutrophil recovery, 20 had evidence of full-donor or mixed chimerism (data missing for 1 patient). Overall, 14 patients experienced GF, and 4 of them received a subsequent HSCT (Table 1). Twelve-month survival was similar in patients with or without GF (48% versus 52%), whereas patients who did not achieve neutrophil recovery had poorer survival (14%). Indeed, some patients lived several years with autologous reconstitution and active disease (Table 1). According to the conditioning regimen, 8 of 11 MAC and 20 of 24 RIC achieved neutrophil recovery. Platelet recovery was achieved in 4 MAC and 15 RIC and was higher in patients who underwent splenectomy before UCBT (40% versus 70%, $P = .02$). Importantly, all patients receiving TCF as conditioning achieved both neutrophil and platelet recovery. Cell dose, disease characteristics, age, or cytomegalovirus serostatus had no significant impact on engraftment.

Graft-versus-Host Disease

Ten patients developed grades II to IV acute GVHD (7 grade II, 2 grade III, 1 grade IV) with a median time of onset of 33 days (range, 14 to 94). Among 18 patients at risk for chronic GVHD, 6 developed limited and 1 extensive chronic GVHD, with a median onset time of 167 days (range, 91 to 328).

Disease Status

Overall, 15 patients experienced progressive disease or relapse at a median of 7 months (range, 1 to 31) after UCBT: 3 were originally diagnosed with AML (in first complete remission at UCBT), 6 with PMF, and 6 with SMF (Table 1). Among patients with relapse, 7 had GF. One patient with AML relapsed 2.5 years after UCBT and received a second allogeneic HSCT from a matched unrelated donor, dying of veno-occlusive disease 92 days later. Among 11 patients alive at least 6 months after UCBT without relapse, 3 had available marrow biopsy results: 1 had complete resolution of marrow fibrosis (grade 0 at 21 months), 1 regressed from grade III to I

Table 1
Patients, Disease and Transplant Characteristics, and Causes of Death

	Gender and Age	Diagnosis JAK2-V617 F Mutation	Prognostic Scores: Lille at Diagnosis [16] DIPSS at UCBT [17]	Splenectomy Degree of BM Fibrosis*	Time from Diagnosis of MF to UCBT (mo)	Type of Graft TNC ($\times 10^7$)/CD34 ($\times 10^5$)/kg at Collection	Conditioning Regimen	Recovery Delay (d): Neutrophils/Platelets Chimerism	State	Main Cause of Death	Follow-up from UCBT (d)
1	Male 31	PMF -	Low High	Yes Severe	27	Single CB 2.8/.22	RIC: other ATG	21/35 unknown	Dead	MF	137
2	Female 51	PMF -	High High	Yes Severe	27	Single CB 3.94/.91	MAC: other	-/- not done	Dead	Septic shock after infusion of autologous HSC	34
3	Female 58	ET SMF -	Intermediate High	Yes Moderate	7	Single CB 4.63/1.39	RIC: TCF ATG	25/37 mixed	Dead	Cerebral hemorrhage	147
4	Male 52	ET SMF mutated	Intermediate Intermediate-2	No Severe	1	Double CB 6.38/1.55	RIC: other ATG	-/- autologous reconstitution	Dead	MF continuous progression even after a second UCBT performed for rejection	140
5	Male 27	ET SMF mutated	Low Low	Yes -	7	Double CB 3.58/-	MAC: TCF	27/34 full donor	Dead	MF	1480
6	Male 59	PMF mutated	High -	Yes Moderate	29	Double CB 4.3/1.87	MAC: TCF	35/90 full donor	Alive in Remission		1592
7	Male 47	PMF wild type	High Intermediate-2	No Mild	5	Double CB 5.7/2.19	RIC: TCF	41/69 full donor	Alive in Remission		1321
8	Female 36	PMF wild type	Intermediate Intermediate-1	No Severe	82	Single CB 3.3/.56	MAC: other	44/- autologous reconstitution	Alive with MF		2198
9	Male 62	PMF -	Intermediate -	No -	10	Double CB 3.54/2.01	RIC: other	-/- not done	Dead	Infection + ARDS	21
10	Male 51	PMF -	Low Low	Yes Severe	41	Double CB 6.04/2.69	MAC: other ATG	21/19 autologous reconstitution	Dead	Bacterial infection	2074
11	Male 49	PMF -	Intermediate -	Yes Severe	13	Double CB 3.75/1.28	RIC: TCF	37/85 full donor	Dead	MF	1072
12	Male 61	MPN/MDS SMF mutated	Intermediate Intermediate-2	No Moderate	10	Double CB 4.15/1.32	RIC: TCF	60/91 full donor	Dead	EBV-related PTLD	284
13	Male 54	ET SMF -	Intermediate Intermediate-1	No Moderate	8	Single CB 3.4/1.5	RIC: other ATG	31/- full donor	Dead	MF	83
14	Male 54	ET SMF wild type	- Intermediate-1	No Severe	30	Single CB 3.97/2.32	RIC: other ATG	28/- full donor	Dead	Acute GVHD	61
15	Male 37	PMF mutated	Intermediate Intermediate-2	Yes Severe	12	Double CB 4.75/1.46	RIC: other ATG	36/42 autologous reconstitution	Dead	MF	400
16	Female 63	PMF wild type	Low Intermediate-2	Yes -	150	Double CB 4.41/.79	RIC: TCF	17/17 mixed	Alive in Remission		1083
17	Male 56	PV SMF mutated	High Intermediate-2	Yes Moderate	4	Single CB 4.72/3.71	RIC: TCF	10/13 autologous reconstitution	Dead	MF	1969
18	Female 43	ET SMF mutated	Intermediate Intermediate-2	Yes -	23	Double CB 4.79/1.5	RIC: TCF ATG	11/18 mixed	Alive with MF		1855
19	Male 57	PMF wild type	- Intermediate-2	Yes -	79	Double CB 4.37/1.89	RIC: TCF ATG	51/- mixed	Dead	EBV-related PTLD	77
20	Female 54	PMF mutated	Low High	Yes -	85	Double CB 5.41/-	RIC: TCF	33/62 mixed	Dead	MF	351
21	Male 60	ET SMF wild type	Low Intermediate-1	Yes Severe	111	Double CB 5.06/1.56	RIC: other ATG	23/- full donor	Dead	Pulmonary infection	118
22	Female 38	PMF -	Intermediate -	No Severe	20	Double CB -/-	RIC: other ATG	36/50 autologous reconstitution	Alive with MF		658
23	Male 58	PMF wild type	High High	No Severe	7	Double CB 8.58/4.76	MAC: TCF	30/- mixed	Alive in remission		702

(*continued on next page*)

Table 1
(*continued*)

	Gender and Age	Diagnosis JAK2-V617 F Mutation	Prognostic Scores: Lille at Diagnosis [16] DIPSS at UCBT [17]	Splenectomy Degree of BM Fibrosis*	Time from Diagnosis of MF to UCBT (mo)	Type of Graft TNC ($\times 10^7$)/CD34 ($\times 10^5$)/kg at Collection	Conditioning Regimen	Recovery Delay (d): Neutrophils/Platelets Chimerism	State	Main Cause of Death	Follow-up from UCBT (d)
24	Male 54	PMF wild type	Intermediate High	No Mild	12	Single CB 4.54/2.65	RIC: other ATG	-/- autologous reconstitution	Dead	Infection	53
25	Female 56	PV SMF mutated	- High	Yes -	26	Double CB 6.76/2.03	RIC: other ATG	-/- autologous reconstitution	Dead	MOF after a second UCBT performed for rejection	233
26	Female 51	PMF wild type	High Intermediate-2	No Moderate	14	Single CB -/-	MAC: other ATG	-/- autologous reconstitution	Alive in remission after a second HSCT (MUD) performed for rejection		413
27	Female 58	ET SMF wild type	Low Intermediate-2	No Moderate	7	Double CB 5.92/3.73	RIC: TCF	35/55 autologous reconstitution	Alive with MF		192
28	Female 49	PMF wild type	High Intermediate-1	No Moderate	28	Single CB 5.25/3	RIC: other ATG	16/62 full donor	Dead	Infection	126
29	Male 40	ET SMF>>AML -	Low NE	No Severe	63	Single CB 1.74/.23	MAC: other ATG	30/30 full donor	Dead	VOD after a second HSCT (MUD) performed for AML relapse	1073
30	Male 58	PMF>>AML mutated	- NE	No -	51	Double CB 4.24/.84	MAC: TCF	17/- autologous reconstitution	Dead	AML	60
31	Female 58	PV SMF>>AML mutated	Low NE	No Severe	11	Double CB 4.26/1.66	RIC: TCF	20/38 mixed	Alive in remission		651
32	Male 42	PMF>>AML mutated	High NE	No Severe	29	Double CB 6.83/2.26	RIC: TCF	37/- full donor	Dead	ARDS	144
33	Male 44	ET SMF>>AML wild type	High NE	No -	104	Single CB 3.63/1.34	MAC: other ATG	31/- full donor	Dead	AML	445
34	Male 60	ET SMF>>AML wild type	Low NE	No -	8	Double CB 4.32/2.18	MAC: other ATG	-/- autologous reconstitution	Dead	Acute GVHD after a second UCBT performed for rejection	213
35	Female 60	PMF>>AML wild type	High NE	No Moderate	5	Single CB 4.92/2.03	RIC: TCF	22/48 full donor	Alive in remission		206

DIPSS indicates dynamic international prognostic scoring system; TNC, total nucleated cells; BM, bone marrow; CB, cord blood; ATG, antithymoglobulin; ET, essential thrombocythemia; MPN/MDS, myeloproliferative/myelodysplastic syndrome; ARDS, acute respiratory distress syndrome; EBV, Epstein-Barr virus; PTLD, post-transplant lymphoproliferative disease; PV, polycythemia vera; MOF, multiorgan failure; MUD, matched unrelated donor; NE, not assessable; VOD, veno-occlusive disease.

* According to the European Consensus on Grading Bone Marrow Fibrosis (2005) [18].

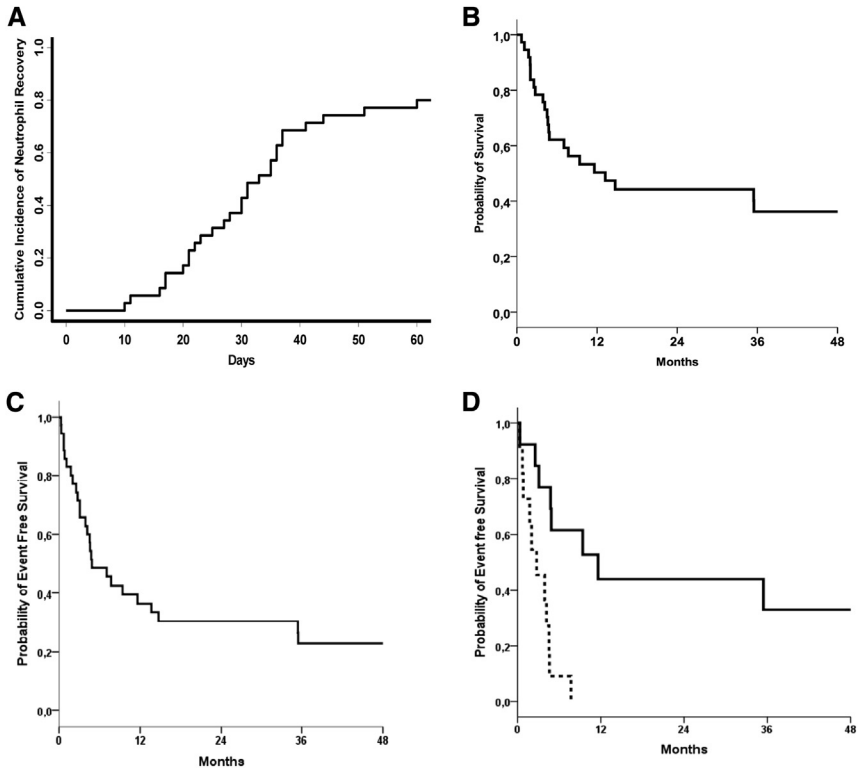

Figure 1. Outcome of patients with MF after UCBT. (A) Cumulative incidence of neutrophil recovery (60-day = 80%, n = 28). (B) Probability of OS (2-year = 44%, n = 16). (C) Probability of EFS (2-year = 30%, n = 10). (D) Probability of EFS in the RIC population (n = 24) according to the conditioning regimen (—, TCF; . . . ., others: 2-year = 44% versus 0%, $P = .001$).

(after 12 months), and 1 regressed from grade II to I (after 9 months).

TRM, OS, and EFS

Overall, 24 patients died: 10 of relapse and 14 of transplant-related causes, detailed in Table 1. The median follow-up was 24 months (range, 6 to 73). The cumulative incidence of TRM at 2 years was 35%. The 2-year OS and EFS rates were 44% and 30%, respectively (Figure 1B,C). In univariate analysis, age, time from diagnosis to transplantation, number of cord blood units infused, cell dose, and disease characteristics had no significant impact on EFS or OS. According to diagnosis, EFS was 35% for PMF, 18% for SMF, and 36% for AML. Among the 24 patients given RIC, those who received TCF (n = 13) had a significantly higher EFS (44% versus 0%, $P = .001$; Figure 1D), whereas in patients receiving MAC, no significant difference was found according to the type of conditioning regimen used.

DISCUSSION

In this study we describe patients receiving UCBT for PMF or SMF. We selected our cases from the Eurocord registry, a large international registry for UCBT, to which only 35 cases were reported from 23 centers over an 8-year period, confirming that UCBT is rarely performed in patients with MF. These patients were at high risk at UCBT because of the advanced disease stage (20% had MF in blast phase). The median age at UCBT was relatively high, similar to that reported in patients having received a graft from an adult unrelated donor. In our series GF was a major concern. The lower engraftment rate could be explained by the association of the underlying disease and the stem cell source, which are both well-known independent risk factors for delayed engraftment and GF. Nevertheless, 2 observations can be highlighted in our population: patients who experienced GF but achieved neutrophil recovery had prolonged survival, and patients who received a TCF-based conditioning had an excellent engraftment. Importantly, 13 of 17 patients receiving TCF had a RIC regimen, which may have contributed to the improved results in this advanced-age population in terms of both engraftment and EFS.

In our results patients who never achieved neutrophil recovery had poorer survival. One may argue that this finding may be correlated with the type of conditioning used. Unfortunately, in our study we were unable to explore this finding further because we were dealing with small subgroups of patients. No other prognostic factors were identified, including cell dose. However, it is important to note that 32 of 33 assessable patients received an adequate dose of total nucleated cells ($\geq 2.5 \times 10^7$/kg).

As previously described in other HSCT settings, we demonstrated that it is possible to obtain regression of bone marrow fibrosis after UCBT. Furthermore, some patients had long-term survival, despite particularly adverse prognostic features (age, advanced disease stage), and we observed encouraging results for cases of leukemic transformation that would otherwise have an expected survival of 4 months in the absence of HSCT [15].

The role of JAK2 inhibitors in the MF treatment pathway has yet to be determined. In our study only 1 patient with

PMF was treated with JAK2 inhibitors before UCBT. Therefore, we were not able to draw any conclusion in this specific setting.

In conclusion, our results suggest that UCBT is feasible for patients with MF. However, the interpretation of these results was limited by the small sample size and the retrospective registry-based nature of the study; therefore, larger trials are needed to identify specific risk factors. The selection of cord blood units with higher numbers of cells or the use of double-UCBT, associated with a TCF-based RIC regimen, should be further explored to improve outcomes in this particular subset of patients.

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Authorship statement: M.R. and F.G. co–first authors. M.R., A.R., and V.R. designed the study. F.G. collected data and performed the statistical analysis. M.R., F.G., E.G., and A.R. wrote the article. E.D., M.M., M.M., G.S., P.C., J.Y.C., F.L., M.R., J.P., J.S., S.N., N.M., I.Y.A., W.L., P.C., M.M., and J.O.B. contributed to patients. All authors edited and approved the manuscript.

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