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Full Length Article
Cord Blood

Umbilical Cord Blood Transplantation after Graft Failure from a Previous Hematopoietic Stem Cell Transplantation

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A B S T R A C T

Graft failure (GF) is a life-threatening complication after allogeneic hematopoietic stem cell transplantation (HCT). In the absence of autologous recovery, a second HCT is necessary to attempt to prevent death due to prolonged pancytopenia. Previous studies describing outcomes of second HCT performed after GF with different types of donor sources report wide ranges of overall survival (OS) and transplantation-related mortality (TRM); however, studies including a large number of patients undergoing a second HCT with umbilical cord blood (UCB) as the graft source are scarce. This retrospective registry-based study examined data extracted from Eurocord and the European Society for Blood and Marrow Transplantation (EBMT) databases to evaluate outcomes of 247 UCBTs performed in EBMT transplant centers after GF following a previous HCT. Data were analyzed separately for patients with malignant diseases (n = 141) and those with nonmalignant diseases (n = 106). The most frequent HCT that resulted in GF was also UCBT (65.0% for patients with malignant diseases and 68.9% for those with nonmalignant diseases), and most GFs occurred within 100 days after transplantation (92.3% and 85.9%, respectively). The median follow-up was 47 months for surviving patients with malignant diseases and 38 months for those with nonmalignant diseases. We observed a similar cumulative incidence of neutrophil engraftment of 59.1% (95% confidence interval [CI], 51.4% to 67.9%) and 60.4% (95% CI, 51.7%-70.6%), respectively, at a median time of 23 days and 24 days, correspondingly. The 3-year OS was 28.9% (95% CI, 21.8% to 37.3%) in the malignant disease group and 49.1% (95% CI, 39.5%-58.8%) in the nonmalignant disease group. In patients with malignancies, TRM was 39.9% (95% CI, 32.5% to 49.1%) at 100 days and 57.5% (95% CI, 49.4%-66.8%) at 3 years. In multivariate analyses, none of the characteristics studied was statistically significantly associated with engraftment or OS. Although survival is not optimal in patients requiring a second HCT, UCBT remains a valid life-saving option for patients with GF.

INTRODUCTION

Graft failure (GF) is a severe complication after hematopoietic stem cell transplantation (HCT), usually associated with dismal survival [1]. The incidence of GF after HCT using HLA-matched donors is <5% [2,3]; however, a higher incidence is

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observed with HLA-mismatched donors or alternative donor sources, as well as with the use of reduced-intensity conditioning (RIC) regimens [4–6].

Several mechanisms may be involved in GF, including hematopoietic stem cell damage during processing and thawing procedures, immunologic factors such as HLA or ABO mismatch, insufficient cell dose, bone marrow microenvironment, use of an RIC regimen, viral infections, bone marrow toxicity, and graft-versus-host-disease (GVHD), among others [7].

The risk of GF may vary according to disease and is particularly worrisome in disorders in which patients are heavily transfused prior to HCT [8]. Moreover, the presence of HLA donor-specific antibodies (DSA) might mediate graft rejection [9,10]. This is a serious concern in haploidentical, other HLA-mismatched HCT and umbilical cord blood transplantation (UCBT) settings, but it potentially could be circumvented with different strategies to detect and remove DSA before transplantation [9,10].

GF needs to be recognized early and managed appropriately, as prolonged aplasia increases the risk of potential life-threatening infections [11]. Strategies for GF management are challenging and include the use of growth factors, stem cell boosts, and often a new HCT [12].

Previous studies have described outcomes of second HCTs performed after GF, reporting wide ranges of overall survival (OS) and transplantation-related mortality (TRM) [3,13-23]. However, large studies describing salvage UCBT are still needed.

UCB grafts are readily available, allowing for timely new transplantation [24]. In the present study, we evaluated the outcomes of UCBT in patients who experienced GF after a previous HCT.

METHODS

Study Population and Design

The study population included 247 patients with malignant or nonmalignant hematologic diseases who underwent unrelated UCBT at a European Society for Blood and Marrow Transplantation (EBMT) center between 2004 and 2019, after experiencing primary or secondary GF following a previous HCT.

This retrospective descriptive study was conducted using data from Eurocord and EBMT registries in accordance with the Declaration of Helsinki. Patients or legal guardians provided informed consent. The Institutional Review Board of Eurocord approved the study.

Study Objective, Definitions, and Endpoints

The study objective was to describe unrelated UCBTs in patients who failed to engraft or experienced GF after a previous HCT with any donor source. UCBTs provided as salvage treatment for GF as well as those performed later in the course of disease (in patients with autologous reconstitution) were included.

Primary GF was defined as never achieving neutrophil engraftment after HCT or losing the graft within 100 days after the procedure. Secondary GF was defined as graft loss after day +100 post-transplantation with or without autologous recovery.

HLA matching was defined considering HLA antigen level for HLA-A and HLA-B and allele level for HLA-DRB1. A myeloablative conditioning regimen was defined as a regimen containing either total body irradiation (TBI) at $\geq$6 Gy or a busulfan dose of >8 mg/kg orally or >6.4 mg/kg i.v. Other conditioning regimens were defined as RIC. The primary endpoint was neutrophil engraftment at 60 days post-UCBT, defined as the first of 3 consecutive days of an absolute neutrophil count $\geq 0.5 \times 10^9$/L.

Secondary endpoints were OS, acute GVHD (aGVHD) and chronic GVHD (cGVHD), disease-free survival (DFS), relapse/progression, and TRM. (DFS, relapse. and TRM were considered for the malignant disease cohort only.) Diagnosis and grading of aGVHD and cGVHD were performed according to standard criteria [25]. TRM was defined as death not preceded by relapse, and DFS was defined as survival without relapse.

Statistical Analysis

We examined UCBT outcomes for patients with malignant (n = 141) and nonmalignant diseases (n = 106) separately.

Percentages were reported for categorical variables, and median values with ranges were reported for continuous variables. Univariate analyses (UVAs) were performed using Gray's test for cumulative incidence functions (CIFs) of neutrophil engraftment, TRM, grade II-IV aGVHD, cGVHD, and relapse; and using the Kaplan-Meier estimator for the probabilities of OS and DFS, with log-rank test applied for comparisons. Death was considered a competing event for GVHD and engraftment, and TRM was considered a competing risk for relapse and vice-versa.

Multivariate analyses (MVAs), when applicable, were performed using Cox proportional hazards regression models. Variables that reached a *P* value of .10 in UVA were considered in initial MVA models, along with other variables of clinical interest (diagnosis and interval between HCT resulting in GF and UCBT). Variables with too many missing values were excluded from final MVA models. All *P* values were 2-sided, and the type I error was fixed at 0.05. Statistical analyses were performed using R (R Core Team) and SPSS (IBM).

RESULTS

Malignant Diseases

Patient and transplantation characteristics

Patient and UCBT characteristics of the 141 patients (males, n = 83; females, n = 58) with malignant diseases are provided in Table 1. The most frequent diagnosis was acute leukemia (64.5%; acute myelogenous leukemia, n = 50; acute lymphocytic leukemia, n = 34).

The median age at UCBT was 29.1 years (range, 0.9 to 69.7 years), and 63.1% of the patients were adults (age $\geq$18 years). The reason for the rescue UCBT was primary GF in 92.3% of the patients.

More than one-half of the patients (53.2%; n = 75) underwent single UCBT for the rescue transplant. RIC regimen was used in 90.2% of the patients, with cyclophosphamide + fludarabine $\pm$ TBI the most frequently reported regimen (52.5%). Fifty-eight patients (50.9%) received in vivo T cell depletion. More than one-half (57.8%) of the patients had 2 HLA mismatches with their UCB graft. The median duration of follow-up for live patients was 47 months.

Characteristics of the HCT that resulted in GF

The graft source for the previous HCT was unrelated single-unit UCB in 69 patients, unrelated double-unit UCB in 22, related peripheral blood stem cells (PBSCs) in 9, unrelated PBSCs in 19, related bone marrow (BM) in 5, unrelated BM in 7, and unknow combination of donor type and graft source in 10. Twelve patients underwent 2 HCTs before UCBT. The median interval between the HCT that resulted in GF and the rescue UCBT was 57 days (range, 16 to 365 days). Conditioning regimen information for the failed HCTs is provided in Table 2.

Outcomes

The CIF of engraftment at 60 days was 59.1% (95% confidence interval [CI], 51.4% to 67.9%). The median time to neutrophil engraftment was 24 days (range, 11 to 85 days). Autologous reconstitution after the salvage UCBT was reported in 12 patients. The results of UVA for engraftment and other outcomes are provided in Supplementary Table S1, and those of MVA are provided in Table 3.

Acute GVHD grade II-IV was observed in 36 patients (grade II, n = 17; grade III, n = 8; grade IV, n = 11), and the CIF of aGVHD grade II-IV at 100 days was 27.3% (95% CI, 20.6% to 36.1%). The CIF of cGVHD at 3 years was 14.5% (95% CI, 8.7% to 24.1%), and 8 of the 13 patients who developed cGVHD had the extensive form. The median time of onset of aGVHD and cGVHD was 35 and 128 days, respectively.

The 3-year CIF of relapse was 15.3% (95% CI, 10.2% to 23.1%), at a median time from UCBT of 82 days (range, 8 to 715 days).

The CIF of TRM was 39.9% (95% CI, 32.5% to 49.1%) at 100 days and 57.5% (95% CI, 49.4% to 66.8%) at 3 years. The

Table 1
Patient and UCBT Characteristics

Characteristics	Malignant Disease Group (N = 141)[†]		Nonmalignant Disease Group (N = 106)[†]	
Sex, n (%)				
Female	58	(41.1)	46	(43.4)
Male	83	(58.9)	60	(56.6)
Diagnosis, n (%)				
Acute leukemia	91	(64.5)	-	
MDS	19	(13.5)	-	
MPD	17	(12.1	-	
Combined MDS/MPD	7	(5.0)	-	
PTLD	6	(4.3)	-	
Plasma cell disorder	1	(0.7)	-	
IEM	-		40	(37.7)
BMF syndrome	-	-	36	(34.0)
PID	-	-	23	(21.7)
Hemoglobinopathy	-	-	5	(4.7)
Histiocytic disorder	-	-	2	(1.9)
Remission status at UCBT, n (%)				
No CR	31	(27.2)	NA	
CR	83	(72.8)	NA	
Children (<18 yr), n (%)	52	(36.9)	91	(85.8)
Adults (≥18 yr), n (%)	89	(63.1)	15	(14.2)
Age at HCT, yr, median (range)	29.1 (0.9-69.7)		5.4 (0.5-51.8)	
Weight, kg, median (range)	56 (7.2-105)		17 (4.5-73)	
Time from diagnosis to UCBT, mo, median (range)[‡]	12.1 (2.1-248.5)		27.4 (2.17-238.42)	
CMV seropositivity, n (%)	72	(59.5)	54	(56.8)
Previous allogeneic HCTs, n (%)				
1	129	(91.5)	95	(89.6)
2	12	(8.5)	10	(9.4)
3	-		1	(0.9)
Year of UCBT, median (range)	2011 (2004-2019)		2012 (2005-2019)	
Graft type, n (%)				
Single UCB	71	(50.4)	89	(84.0)
Intrabone single UCB	4	(2.8)	0	
Double UCB	66	(46.8)	17	(16.0)
Serotherapy (ATG or mAb), n (%)	58	(50.9)	77	(84.6)
Conditioning regimen intensity, n (%)				
RIC	119	(90.2)	69	(74.2)
MAC	13	(9.8)	24	(25.8)
Conditioning regimen components, n (%)				
Cy + Flu	61	(52.5)	30	(33.7)
Flu	19	(16.5)	7	(17.9)
Flu + other	28	(24.1)	39	(43.8)
Cy + Bu	3	(2.6)	7	(7.9)
Other	5	(4.3)	6	(6.7)
TBI	60	(45.5)	23	(23.7)
GVHD prophylaxis, n (%)				
CSA + MMF ± other	63	(52.0)	35	(36.8)
CSA	25	(20.7)	17	(17.9)
CSA + other	19	(15.7)	0	
CSA + prednisolone	0		35	(36.8)
Other	14	(11.6)	8	(8.5)
Infused TNC dose, $\times 10^7$/kg, median (range)	4.24 (1.4-25.3)		6.6 (1.4-88)	
Infused $CD34^+$cell dose, $\times 10^5$/kg, median (range)	1.72 (0.18-12.7)		2.1 (0.03-29.5)	
Donor/recipient HLA mismatch, n (%)				
0/6	10	(8.6)	12	(14.8)
1/6	27	(23.3)	36	(44.4)
2/6	67	(57.8)	31	(38.3)
3/6	12	(10.3)	2	(2.5)

(*continued*)

Table 1 (*Continued*)

Characteristics	Malignant Disease Group (N = 141)[†]		Nonmalignant Disease Group (N = 106)[†]	
Donor/recipient sex match, n (%)[§]				
Female/female or male/male	52	(38.2)	41	(42.7)
Female/male or male/female	84	(61.8)	55	(57.3)
Donor/recipient ABO match, n (%)[¶]				
Compatible	39	(33.9)	17	(28.8)
Minor ABO incompatibility	34	(29.6)	15	(25.4)
Major ABO incompatibility	42	(36.5)	27	(45.8)
Time between previous HCT and UCBT, d, median (range)	57 (16-365)		65.5 (28-759)	
Follow-up for survivors, mo, median (range)	46.9 (1.1-167.5)		38.2 (1.6-169.9)	

MDS indicates myelodysplastic syndrome; MPD, myeloproliferative disorder; CR, complete remission; NA, not applicable; CMV, cytomegalovirus; ATG, antithymocyte globulin; MAC, myeloablative conditioning; Cy, cyclophosphamide; Flu, fludarabine; Bu, busulfan; CSA, cyclosporine A; MMF, mycophenolate mofetil; TNC, total nucleated cells.

[†] Missing data: Malignant diseases- CMV, n = 20; conditioning regimen intensity, n = 9; conditioning regimen drugs, n = 25; GVHD prophylaxis, n = 20; HLA mismatch, n = 25; infused TNC, n = 29; infused $CD34^+$ cells, n = 32; previous allogeneic HCT, n = 2 (the 2 patients with missing information had at least 1 previous HSCT); remission status, n = 27; serotherapy, n = 27; TBI, n = 9; donor-recipient gender match, n = 5; donor-recipient ABO match, n = 26; weight, n = 23. Nonmalignant diseases- $CD34^+$, n = 38; CMV, n = 11; conditioning regimen drugs, n = 17; conditioning regimen intensity, n = 13; GVHD prophylaxis, n = 11; HLA mismatch, n = 25; infused TNC, n = 36; donor-recipient gender match, n=10; serotherapy, n=23; TBI, n = 9; weight, n = 35.

[‡] Bone marrow failure syndrome only for nonmalignant diseases.

[§] In case of double units, the categories for donor/recipient sex match are as follows: both units are female/female or male/male, and at least 1 unit is female/male or male/female.

[¶] In case of double units, the categories for donor/recipient ABO match" are as follows: both units are ABO compatible; at least 1 unit has minor ABO incompatibility; and at least 1 unit has major ABO incompatibility.

Table 2
Characteristics of HCT Resulting in GF

Characteristic	Malignant Diseases Group (N = 141)[†]		Nonmalignant Diseases Group (N = 106)[†]	
Stem cell source, n (%)				
Single UCB	69	(49.3)	71	(67.0)
Double UCB	22	(15.7)	2	(1.9)
BM	17	(12.1)	13	(12.2)
PBSC	30	(21.4)	18	(17.0)
Other	2	(1.4)	2	(1.9)
Donor type, n (%)				
Related	14	(10.5)	17	(16.7)
Unrelated	119	(89.5)	85	(83.3)
Serotherapy (ATG or mAb), n (%)	73	(65.8)	89	(92.7)
MAC regimen, n (%)	85	(63.4)	55	(53.9)
Conditioning regimen drugs, n (%)				
Cy + Flu	31	(24.0)	21	(21.4)
Bu + Flu	19	(14.7)	37	(37.8)
Bu + Cy	19	(14.7)	13	(13.3)
Cy	19	(14.7)	5	(5.1)
Other	41	(31.9)	20	(22.4)
TBI, n (%)	63	(47.0)	11	(10.8)
Type of GF, n (%)				
Primary	120	(92.3)	85	(85.9)
Secondary	10	(7.7)	14	(14.1)

[†] Missing data: Malignant disease group- conditioning regimen drugs, n=12; conditioning regimen intensity, n=7; donor type, n=8; serotherapy, n=30; stem cell source, n=1; TBI, n=7; type of GF, n=11. Nonmalignant disease group- conditioning regimen drugs, n = 10; conditioning regimen intensity, n = 4; donor type, n = 4; serotherapy, n=10; TBI, n = 4; type of GF, n = 7.

main cause of death was TRM (n = 79, mainly in patients who failed to engraft after the rescue UCBT [n = 49]) due to infection (n = 28), rejection/infection (n = 15, including 1 Epstein-Barr virus [EBV]-related post-transplantation lymphoproliferative disorder [PTLD]), GVHD (n = 16), multiorgan failure (n = 8), rejection not further specified (n = 4), hemorrhage (n = 3), or other causes (n = 5). Seventeen patients died of relapse.

Of note, 12 patients in the malignant disease cohort required a new HCT after the UCBT described in this report (8 for recurrent GF, 2 for relapse, and 2 for unknown cause).

The 3-year OS was 28.9% (95% CI, 21.8% to 37.3%), and 3-year DFS was 28.4% (95% CI, 21.3% to 36.8%). Survival differed according to diagnosis, with a 3-year OS of 28.4% (95% CI, 19.7% to 39.0%) in patients with acute leukemia; 32.4% (95% CI, 19.2% to 49.1%) in those with myelodysplastic syndrome, myeloproliferative disorder, or combined myelodysplastic syndrome/ myeloproliferative disorder; and 14.0% (95% CI, 2.5% to 50.7%) in those with other diagnoses. The MVA did not show any statistically significant factors associated with OS (Table 3).

Table 3
Multivariate Analyses for the Malignant and Nonmalignant Diseases Groups

Covariate		HR (95% CI)[a]	*P* Value
Malignant diseases group			
Overall survival			
Age	Children	Reference	
	Adults	1.62 (0.97-2.72)	.066
HLA matching	0-1 mismatch	Reference	
	>1 mismatches	1.58 (0.93-2.70)	.094
Diagnosis	Acute leukemia	Reference	
	MDS, MPD, or MDS/MPD	0.72 (0.44-1.18)	.197
	Other	1.64 (0.69-3.95)	.265
Interval between previous HSCT and UCBT*		0.99 (0.99-1.00)	.050
Neutrophil engraftment			
TBI	No	Reference	
	Yes	1.24 (0.75-2.06)	.399
Year of UCBT	≤2011	Reference	
	>2011	1.16 (0.71-1.91)	.556
Remission status at UCBT	No CR	Reference	
	CR	1.89 (0.99-3.62)	.055
Diagnosis	Acute leukemia	Reference	
	MDS, MPD or MDS/MPD	0.64 (0.33-1.24)	.188
	Other	1.34 (0.40-4.43)	.636
Interval between previous HSCT and UCBT*		1.00 (1.00-1.01)	.206
Nonmalignant diseases group			
Neutrophil engraftment			
CMV	No	Reference	
	Yes	0.70 (0.43-1.17)	.172
Year of UCBT	≤ 2011	Reference	
	> 2011	1.37 (0.83-2.26)	.224
Serotherapy (ATG or mAb)	No	Reference	
	Yes	2.37 (0.95-5.96)	.066

*HSCT to UCBT interval (days) considered as a continuous variable.
[a] For overall survival MVA, the HRs indicate the risk of death (HR >1, increased risk of death) and for the MVAs of neutrophil engraftment , the HRs indicate the risk of engrafting (HR >1, improved engraftment).

Nonmalignant Diseases Group

Patient and transplantation characteristics

Table 1 reports the characteristics of the 106 patients (males, n = 60; females, n = 46) with nonmalignant diseases. The most frequent diagnosis in this groups was an inborn error of metabolism (IEM; 37.7%), followed by BM failure syndrome (BMF; 34.0%), primary immune deficiency (PID; 21.7%), and other diagnoses (6.6%).

The median age at UCBT was 5.4 years (range, 0.5 to 51.8 years), and 15% of recipients were adults (BMF, n = 11; PID, n = 2; hemoglobinopathy, n = 1; IEM, n = 1).

Eighty-nine patients (84%) underwent a single UCBT. Most patients received an RIC regimen (74.2%); the most frequently used conditioning regimens in patients with nonmalignant diseases were cyclophosphamide + fludarabine ± TBI (33.7%) or a combination of fludarabine and other drugs (43.8%). In vivo T cell depletion was used in 77 patients (84.6%). Thirty-six patients (44.4% of those with HLA information available) had only 1 HLA mismatch with their UCB graft. The median follow-up was 38.2 months.

Characteristics of the HCT that Resulted in GF

The graft source of the previous HCT was unrelated single-unit UCB in 71 patients, unrelated double-unit UCB in 2, related PBSCs in 12, unrelated PBSCs in 5, related BM in 4, unrelated BM in 7, and unknow combination of donor type and graft source in 5.

The median interval between the previous HCT and UCBT was 65.5 days (range, 28 to 759 days). Conditioning regimen information for the failed HCTs is provided in Table 2.

Ten patients had undergone 2 HCTs and 1 patient had undergone 3 HCTs before the UCBT reported in this study.

Outcomes

The CIF of engraftment at 60 days was 60.4% (95% CI, 51.7% to 70.6%), at a median of 23 days (range, 6 to 100 days). Thirteen patients experienced autologous recovery after the new UCBT. Diagnoses at transplantation of the patients who failed to engraft or rejected the graft were BMF in 15 patients, hemoglobinopathy in 3, IEM in 12, PID in 7, and histiocytic disorder in 1. Twelve patients who failed to engraft after the salvage UCBT were alive at a median follow-up of 26.8 months (range, 3 to 157.3 months), 5 of them after undergoing a new HCT. The remaining patients (BMF, n = 14; IEM, n = 5; PID, n = 5; hemoglobinopathy, n = 1; histiocytic disorder, n = 1) died, at a median of 36.5 days (range, 3.0 to 930.2 days) after UCBT.

The results of UVA for neutrophil engraftment and OS are provided in Supplementary Table S2, and MVA results are provided in Table 3.

Eighteen patients developed aGVHD grade II-IV (grade II, n = 8; grade III, n = 6; grade IV, n = 4). The CIF of aGVHD grade II-IV at 100 days was 17.1% (95% CI, 11.0% to 26.3%). cGVHD occurred in 15 patients, 5 with an extensive form. The CIF of cGVHD at 3 years was 22.1% (95% CI, 14.0% to 34.0%). The median time of onset was 37 days for aGVHD and 172 days for cGVHD.

Overall, 52 patients died (26 of them after failing to engraft). The specific causes of death reported were infection (n = 17, including 2 EBV-related PTLD), GVHD (n = 8), rejection/infection (n = 10, including 1 EBV-related PTLD), rejection not further specified (n = 2), multiorgan failure (n = 2), disease progression (n = 6), and other causes (n = 7).

The 3-year OS was 49.1% (95% CI, 39.5% to 58.8%). Survival differed according to diagnosis, with a 3-year OS of 65.4% (95% CI, 48.9% to 78.9%) in patients with IEM, 52.2% (95% CI, 30.5% to 73.1%) in patients with PID, and 35.4% (95% CI, 21.9% to 78.9%) in patients with BMF (*P*= .020).

DISCUSSION

GF is a major concern after HCT, associated with high mortality [26,27]. A subsequent HCT is often required after GF, and UCBT is a suitable option in such situations where delaying the new transplantation might compromise the patient's survival.

Our results show that despite a previous GF, approximately 60% of patients engrafted after undergoing the new UCBT.

The MVA for patients with malignant diseases revealed a trend toward better engraftment in those who underwent transplantation in complete remission; this finding agrees with previous studies reporting an increased risk of GF in

patients who underwent transplantation with advanced disease status [5,26].

We observed a 3-year OS of 28.9% in patients with malignant diseases and 49.1% in those with nonmalignant diseases. Onishi et al. [21] reported a 45.5% rate of neutrophil engraftment and an OS of 38.8% at 4 years after unrelated UCBT performed in 22 patients with nonmalignant disease with GF. Likewise, a Japanese group reported the feasibility of RIC UCBT as salvage therapy for GF, observing a 74% engraftment rate and 33% 1-year survival in 80 adults with hematologic malignancies [3].

Survival is considerably lower in patients who experience GF after an HCT than in other HCT recipients [27]. Nonetheless, the OS observed in our study is in line with the previous reports on UCBT and some other studies using other graft sources as salvage treatment for GF [3,13,14,19,21,22,28].

Ferra et al. [14] studied the outcomes of 80 patients who received second allogeneic HCT for GF and reported a 5-year OS after the rescue HCT of 28% and a TRM of 47%. Similarly, in a retrospective study of 82 patients, the French Society of Bone Marrow Transplantation and Cell Therapy reported a 3−year OS of 30% and 100-day TRM of 53% after second HCT for GF, with better results in patients who received cyclosporin A for GVHD prevention and had a longer interval between the 2 HCTs [13]. In our study, the majority of the GFs reported occurred within the first 100 days after the first HCT, and thus the interval between transplantations more likely represents a surrogate measure for the time that the patient remained in aplasia, probably offsetting any positive effect of having more time between transplantations. In fact, once the GF is identified, and in the absence of autologous recovery, proceeding with salvage HCT quickly is critical to shorten the period of aplasia and reduce the associated risks of infection and hemorrhage [29].

A less encouraging survival of 11% at 1 year, despite an engraftment rate of 66%, was reported in a study by the Center for International Blood and Marrow Transplant Research that included 122 allogeneic recipients of a second HCT for primary GF [15]. That study differed from our present study by excluding patients who underwent UCBT and patients with evidence of engraftment after their first HCT.

In patients with nonmalignant diseases, survival differed considerably according to diagnosis. Of note, 6 of the 13 patients with BMF who did not engraft after the salvage UCBT and died had severe aplastic anemia (SAA). Patients with SAA are at a higher risk for GF after HCT owing to exposure to multiple transfusions before transplantation as well as to autoimmunity, and outcomes of salvage transplantation in these patients are usually poor [30].

Determining which graft source to use as salvage HCT is not always easy.

In a study comparing stem cell sources (PBSCs, n = 24; BM, n = 16; UCB, n = 180) used in second HCT after a failed UCBT, patients who received PBSCs had a higher incidence of GVHD than those who received UCB [22]. On the other hand, they had a lower incidence of TRM and higher OS, suggesting that PBSCs was a preferable stem cell source for salvage HCT in the context of that study. However, it is important to note that the reported results were based on a very small number of rescues performed with BM and PBSCs compared with UCB.

The most appropriate stem cell source for salvage transplants after a failed HCT from any graft source remains controversial and depends on multiple factors, including donor availability.

Similarly to UCB, related haploidentical donor grafts can be procured readily and can be used for salvage treatment in patients with GF [16,17,19,23,31]. A large Japanese study comparing haploidentical and UCB salvage transplantation after GF found a lower TRM after haploidentical transplantation (45.1% vs 49.8%) but comparable survival with the 2 approaches [19].

Infection was the main cause of death reported in our study. The risk of infection is particularly high in patients who failed a previous transplantation owing to GF caused by prolonged aplasia. However, we postulate that TRM could be reduced through improved engraftment and advancements in antimicrobial microbial prophylaxis.

Strategies to improve engraftment after UCBT include selecting UCB units with optimal HLA matching and an adequate cell dose, screening patients for DSA, performing intrabone infusion of UCB grafts, and using growth factors and cytokines [32]. In addition, novel approaches for improving BM homing capacity and off-the-shelf expanded UCB units might be attractive in this setting.

There are some limitations to our study, owing mostly to its retrospective registry-based nature. DSA data were not available in our registry, preventing us from determining whether this factor might have been correlated with further graft rejection, as has been demonstrated in other studies [10,33]. In the patients with malignant diseases, all those who underwent transplantation in complete remission and relapsed before the reported GF were excluded from the study; however, we cannot dismiss the possibility that some nonreported relapses might have introduced some minor selection bias to our population.

Of note, for most of the patients included in the present study, the transplantation that resulted in GF (Table 2) was performed with UCB. This information might be biased, considering that a center that performs UCBT for the first HCT probably will be more likely to perform another UCBT as rescue. Despite these limitations, however, our study contributes to the available literature on second transplantations after GF, providing data for a large number of patients undergoing UCBT and giving separate results for malignant and nonmalignant diseases.

The recent COVID-19 epidemic has affected the daily practice at HCT centers, including donor screening and graft collection [34]. UCB can be readily obtained from cord blood banks to rescue patients experiencing GF when other donors become unavailable owing to epidemics, such as COVID-19, or other emergencies.

Our results show that the use of UCB grafts in patients who experience GF after a previous HCT is feasible. Although the survival prognosis for a patient needing a subsequent transplantation for GF is not optimal, UCBT is usually the sole available alternative in an attempt to save the patient's life. Further studies to decrease transplantation-related toxicity and improve engraftment are needed in an ongoing effort to provide better outcomes for these patients.

DECLARATION OF COMPETING INTEREST

There are no conflicts of interest to report.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2021.10.014.

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