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Full Length Article
Cord Blood

Comparison of Outcomes after UM171-Expanded Cord Blood and Six Conventional Donor Source Transplants: A Matched Analysis from the EBMT Registry

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Cord blood (CB) transplantation has fallen into disfavor because of its association with low cell dose and high non-relapse mortality (NRM). However, a phase I to II trial using UM171-expanded CB transplantation in patients with high-risk hematologic malignancies who lacked a suitable donor demonstrated promising results, including prompt neutrophil engraftment, the ability to use smaller, better human leucocyte antigen (HLA)- matched CB units, and a low NRM rate of 5%. This retrospective matched paired analysis was conducted to test the hypothesis that UM171-expanded CB transplantation provides outcomes

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EBMT
Matched analysis

equivalent or superior to those of conventional hematopoietic stem cell donor sources. The primary objectives were neutrophil engraftment, NRM, and graft versus host disease (GVHD)-free, relapse-free survival (GRFS). This retrospective study compared the outcomes of the 22 adult patients who received a single UM171-expanded CB transplant in the phase I to II trial to those of six cohorts of patients allografted from different stem cell sources, as reported to the European Society for Blood and Marrow Transplantation (EBMT) registry. The six donor control cohorts included: (1) unmanipulated CB, (2) peripheral blood stem cells (PBSC) from a 10/10 HLA-matched unrelated donor (10/10 MUD), (3) bone marrow (BM) from a 10/10 MUD, (4) 9/10 matched unrelated donor (9/10 UD), (5) T cell replete haploidentical (haplo) donor, and (6) HLA- matched sibling donor (MSD). Direct and propensity score matching were used for patient, disease, and transplant characteristics to ensure comparability. The analyzed endpoints included engraftment, GVHD, NRM, relapse, progression-free survival (PFS), overall survival (OS), and GRFS. Neutrophil engraftment was generally similar in all donor groups but was slower for both unmanipulated CB and MUD BM. There was no moderate to severe chronic GVHD in the UM171 CB recipients, with significantly lower rates compared to PBSC MUD, BM MUD, and MSD transplants. PFS, OS, and GRFS were all significantly better with UM171 CB than those seen with haplo donor transplants. GRFS was also consistently superior with UM171 CB when compared to 10/10 MUD PBSC, 9/10 UD, and MSD transplants. UM171-expanded CB recipients have equivalent or improved short- and long-term outcomes compared to patients transplanted from other graft sources.

INTRODUCTION

Cord blood (CB) transplantation has intrinsic challenges due to low cell doses leading to prolonged cytopenias, increased infection risk, extended hospital stays, and higher non-relapse mortality (NRM) compared to other hematopoietic stem cell (HSC) sources [1]. Most CB units are small, compelling physicians to select larger but less well-matched units (only approximately 5% of stored units have an adequate cell dose for adult patients) [2]. These selections increase the number of human leukocyte antigen (HLA) mismatches at loci A, B, C, and DRB1 significantly raising NRM, as previously reported by the Center for International Blood and Marrow Transplant Research (CIBMTR), the European Society for Blood and Marrow Transplantation (EBMT), and Eurocord [3]. Consequently, CB usage as a HSC source has declined over the last decade, largely due to the rise of post-transplant cyclophosphamide (PTCy)-based transplants (from haploidentical [haplo] and mismatched unrelated donors [UD]), perceived as simpler, with fewer engraftment delays and lower NRM rates [1]. However, if the high NRM associated with CB transplantation could be overcome, CB would regain its attractiveness as a HSC source due to its inherently low incidence of chronic graft-versus-host disease (GVHD) without the need for antithymocyte globulin (ATG) or PTCy, and its lower relapse rates particularly in patients with high-risk hematologic diseases [4–6]. Recent reports of higher late relapse incidence with PTCy [7] further underline the potential advantages of CB transplants. To address these limitations, we developed UM171 [8,9], a small molecule promoting cord blood HSC expansion through inhibition of differentiation via degradation of histone deacetylase 1/2 and lysine-specific demethylase 1. Expanded CB has the potential to reduce NRM by shortening the duration of neutropenia and enabling the selection of smaller yet better HLA-matched CB units.

We conducted a first in human phase I to II clinical trial of UM171-expanded CB transplantation at 2 Canadian centers (2016-2018). The trial enrolled patients aged 18 to 65 years without an available HLA-identical donor, including those with high-risk hematologic malignancies and Karnofsky performance status (KPS) $\geq$ 70 [10]. Twenty-two patients received $CD34^+$ selected cells placed into culture for 7 days with UM171 and growth factors, as well as the $CD34^-$ cells, which were cryopreserved and infused into the patient on the day of transplant. Patients underwent a myeloablative or reduced-intensity conditioning regimen. Granulocyte colony-stimulating factor was administered from days 2 post-transplant until engraftment along with GVHD prophylaxis consisting of a calcineurin inhibitor and mycophenolate mofetil. Notably, we observed

rapid neutrophil engraftment with a median of 18 days, despite using small CB units that did not meet conventional minimal cell dose criteria, and no cases of graft failure. Platelet engraftment occurred at a median of 42 days and was achieved in all patients except one who died from early NRM. Furthermore, we observed 100% donor cell chimerism in all cell lineages, superior HLA matching ($\geq$ 6/8 in 82% of patients), improved immune recovery, and a lower risk of moderate to severe infections [10,11]. All these benefits contributed to a remarkably low NRM rate of 4.5%, translating into impressive overall survival (OS) and progression-free survival (PFS) at 1 year: 86% (95% confidence interval [CI], 69% to 97%) and 73% (95% CI, 53% to 89%), respectively, particularly notable since 23% of patients had previously failed an allogeneic (allo) HSC transplant, and 36% had high or very high Disease Risk Index malignancies [12]. Based on these encouraging results, we partnered with the EBMT to conduct a registry-based matched case-control analysis comparing UM171-expanded CB transplantation to six conventional HSC donor sources, in order to test our hypothesis that UM171 yields outcomes equivalent or superior to other HSC sources.

METHODS

Study Design

This retrospective cohort study compared outcomes of 22 patients who underwent single UM171-expanded CB transplantation (February 2016 to November 2018) to matched control cohorts from the EBMT registry who received 6 different types of HSC sources: (1) conventional CB, (2) 10/10 HLA matched unrelated donor (MUD) peripheral blood stem cells (PBSC), (3) 10/10 MUD bone marrow (BM), (4) 9/10 UD PBSC or BM, (5) haplo donor PBSC or BM, and (6) HLA matched sibling donor (MSD) PBSC or BM. EBMT controls were matched to UM171 CB patients using exact and propensity score methods. All EBMT patients provided written informed consent for the use of their anonymized data in research. All UM171 patients were enrolled in a clinical trial approved by the local ethics committee and provided written informed consent for data collection and analysis.

Inclusion/Exclusion Criteria for Controls

Patients were eligible if they had undergone an allo hematopoietic cell transplant (alloHCT) in Europe between 2010 and 2021, had a completed EBMT comprehensive report form, had a diagnosis of acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), myelodysplastic syndrome, chronic myeloid leukemia, non-Hodgkin lymphoma, Hodgkin lymphoma, or chronic lymphocytic leukemia, were aged between 18 and 65 years, had a KPS $\geq$ 70, and received a myeloablative or reduced intensity conditioning regimen. For the CB control group, both single and double CB transplants were allowed, with GVHD prophylaxis consisting of a CNI combined with mycophenolate mofetil. Patients receiving PBSC or BM from sibling donors had to be HLA-matched or haplo, and unrelated donors had to be either 10/10 HLA-matched (10/10 MUD) or 9/10 HLA-matched (9/10 UD). Haplo donor transplants were included only if they were T-cell replete. Exclusion criteria included manipulated grafts, patients who did not consent to research, and CB recipients given ATG or alemtuzumab.

Endpoints

The primary endpoints were neutrophil engraftment (first of 3 consecutive dates with an absolute neutrophil count $\geq 0.5 \times 10^9$/L), NRM, and GVHD-free, relapse-free survival (GRFS). Grade III-IV acute GVHD, extensive or severe chronic GVHD, relapse/progression, or death were events for GRFS [13]. Secondary endpoints included platelet engraftment (first of 3 consecutive dates with platelet count $\geq 20 \times 10^9$/L, unsupported by platelet transfusions for 7 days), PFS, OS, relapse/progression, acute GVHD grades II-IV and III-IV, chronic GVHD, and extensive or severe chronic GVHD.

Matching

The UM171 CB patients were matched to 6 control cohorts from the EBMT database who underwent transplant with (1) single or double unit CB, (2) PBSC from a 10/10 MUD, (3) BM from a 10/10 MUD, (4) BM or PBSC from a 9/10 UD, (5) BM or PBSC from a familial haplo donor, and (6) BM or PBSC from an HLA-matched sibling donor (MSD). Exact matching criteria included disease status at transplant: AML/ALL in 1st complete remission (CR1), 2nd complete remission (CR2), or not in CR; myelodysplastic syndrome/chronic myeloid leukemia; aggressive lymphoma in CR or partial remission (PR) or not in CR/PR; and low-grade lymphoma/chronic lymphocytic leukemia. For the 10/10 MUD PBSC group, exact matching included prior alloHCT, KPS, conditioning regimen, and nearest neighbor for age at transplant. For the other 5 groups, propensity score matching was used for prior alloHCT, age, KPS, and conditioning regimen. Standardized mean difference estimates $<$20% confirmed adequate matching. Matching ratios were

1:3 for MSD, 10/10 MUD PBSC, 9/10 UD, and 1:2 for the other groups. Cases with fewer than 2 or 3 matched controls were retained for analysis.

Statistical Analysis

Descriptive Analysis

Continuous data were summarized using median, minimum, maximum, and interquartile range. All categorical/qualitative data are presented as absolute and relative frequency counts and percentages. No imputation was performed for the missing data.

Comparisons Between Groups

Patient–, disease–, and transplant–related characteristics were compared between UM171 CB and each other source of stem cells using the Chi–squared or Fisher's exact test for categorical variables, and the Mann–Whitney U test for continuous variables. All outcomes were measured from the date of HSC infusion and censored at 2 yr when follow-up differed significantly. The probabilities of OS, PFS, and GRFS were calculated using the Kaplan–Meier method. Relapse/progression and NRM rates were estimated using cumulative incidence functions and considered as competing risks. Cumulative incidence functions were used for neutrophil and platelet recovery as well as for GVHD. Death was the competing event for neutrophil and platelet recovery, while relapse and death were both competing events for GVHD. Outcomes are reported as estimates with 95% CI, including neutrophil and platelet recovery at days 30, 42, 60, and 100; acute GVHD incidence at days 180; and chronic GVHD, relapse/progression incidence (RI), NRM, OS, PFS, and GRFS at 1 and 2 years.

UM171 CB and control groups were compared using a Cox model with cluster-robust standard errors for all analyses, using pair membership as the clustering variable. Results were summarized using hazard ratios (HR) with 95% CI, where an HR <1 favored UM171 CB. All tests are 2–sided with a type I error rate fixed at 0.05. Statistical analyses were performed using R version 4.2.0 (R Core Team, 2020). Patients with missing values were excluded from the propensity score analyses.

Ethics Approval and Consent to Participate

Patients provided written informed consent for research participation. The phase I to II UM171 protocol was approved by the ethics committee of Hopital Maisonneuve Rosemont Hospital (Montreal, Canada).

RESULTS

Overall, 308 controls from the EBMT database were identified: 36 CB, 59 MUD 10/10 PBSC, 31 MUD 10/10 BM, 62 9/10 UD, 59 haplo donors, and 61 MSD. The number of UM171 CB patients in each comparison varied from 17 to 21, depending on the EBMT's capacity to identify at least one control. One UM171 CB patient with refractory, relapsed ALL after prior alloHCT could not be matched to 4 of 6 control groups.

UM171 CB Compared to Conventional CB

Thirty-six conventional CB recipients were compared to 19 UM171 CB transplant patients. Three UM171 patients were excluded due to a lack of a suitable match (2 with prior failed alloHCT). Patient characteristics (Table 1) differed significantly only for median follow-up (36 months for UM171 CB patients versus 75 m for the controls), median year of transplant (2017 for the UM171 cohort and 2015 for the controls), predominant use of tacrolimus in UM171 patients versus cyclosporin in controls, and slightly higher weight in UM171 patients (76 versus 68 kg, P = .052). HLA match data was available for 29 of 36 control patients: 28 received a $\geq$4/6 and 1 a 3/6 HLA-matched CB. Median infused total nucleated and $CD34^+$ cell doses for the controls were 2.7×10^7/kg and 1.5×10^5/kg, respectively; however, CD34+ data were missing for half of the patients. All UM171 CB patients achieved neutrophil engraftment by days 30 as opposed to 69% for the controls (HR: 0.39, 95% CI: 0.23 to 0.66, P = .0005) with median neutrophil engraftment at 18 versus 22 days, respectively (P = .0009, Table 2, Figure 1A). By days 42, 92% of the control group had achieved neutrophil engraftment with 1 case of graft failure, whereas no graft failure was observed among UM171 CB recipients. Time to platelet engraftment, and incidences of acute and chronic GVHD were comparable (Table 3, Figure 1C and S1). NRM was 5% for the UM171 group and 22% for the controls (P = .19, Table 3, Figure 1B). RI, PFS, and OS did not differ significantly between groups (Table 3, Figure 2, and S1). GRFS at 2 years was numerically superior for the UM171 patients (62% versus 41%, HR 0.55; 95% CI: 0.23 to 1.31; Table 3 and Figure 2C) but this difference was not statistically significant.

UM171 CB Compared to PBSC From 10/10 MUD

Fifty-nine 10/10 MUD PBSC recipients were identified as matches for 21 UM171 patients; 1 UM171 patient with refractory relapsed ALL after a 1st alloHCT was excluded. No significant

Table 1
Patient characteristics. Baseline patient characteristics of UM171 expanded cord blood (CB) recipients and six matched cohorts from the European Society for Blood and Marrow Transplantation (EBMT).

Donor comparator		CB			10/10 MUD PBSC			10/10 MUD BM			9/10 UD			Haplo			MSD		
		UM171 CB (n = 19)	CB (n = 36)	*P*	UM171 CB (n = 21)	MUD 10/ 10 PBSC (n = 59)	*P*	UM171 CB (n = 17)	MUD 10/ 10 BM (n = 31)	*P*	UM171 CB (n = 21)	UD 9/10 (n = 62)	*P*	UM171 CB (n = 20)	Haplo (n = 59)	*P*	UM171 CB (n = 21)	MSD (n = 61)	*P*
Follow−up (mo)	Median	36	75	**<.001**	36	42	.14	36	53	**.026**	36.15	39.05	.20	36.15	36.22	.39	36.15	60.18	**.013**
Patient age (years)	Median [IQR]	45 [25−51]	45 [27−51]	.74	45 [27−56]	45 [26−56]	.84	45 [25−55]	43 [25−51]	.58	45 [27−56]	44.3 [25.4−52.1]	.47	44.5 [27−55]	45.1 [25−56]	.98	45 [27−56]	44 [28−52]	.58
Patient sex	Male	12 (63%)	19 (53%)	.46	13 (62%)	39 (66%)	.73	11 (64.7%)	18 (58.1%)	.65	13 (61.9%)	39 (62.9%)	.93	13 (65%)	35 (59.3%)	.65	13 (62%)	40 (67%)	.69
	Female	7 (37%)	17 (47%)		8 (38%)	20 (34%)		6 (35.3%)	13 (41.9%)		8 (38.1%)	23 (37.1%)		7 (35%)	24 (40.7%)		8 (38%)	20 (33%)	
Diagnosis / status	AML CR1	4 (21%)	8 (22%)		4 (19%)	12 (20%)		4 (23.5%)	8 (25.8%)		4 (19%)	12 (19.4%)		4 (20%)	12 (20.3%)		4 (19%)	12 (20%)	
	ALL CR1	4 (21%)	8 (22%)		4 (19%)	12 (20%)		4 (23.5%)	8 (25.8%)		4 (19%)	12 (19.4%)		4 (20%)	12 (20.3%)		4 (19%)	12 (20%)	
	AML CR2	1 (5%)	2 (6%)		1 (5%)	3 (5%)		2 (11.8%)	3 (9.7%)		1 (4.8%)	3 (4.8%)		1 (5%)	3 (5.1%)		1 (5%)	3 (5%)	
	ALL CR2	2 (11%)	4 (11%)		3 (14%)	7 (12%)		2 (11.8%)	4 (12.9%)		3 (14.3%)	9 (14.5%)		2 (10%)	6 (10.2%)		3 (14%)	9 (15%)	
	AML no CR	2 (11%)	4 (11%)		3 (14%)	9 (15%)		4 (23.5%)	8 (25.8%)		3 (14.3%)	9 (14.5%)		3 (15%)	9 (15.3%)		3 (14%)	7 (12%)	
	ALL no CR	1 (5%)	1 (3%)											1 (5%)	2 (3.4%)				
	MDS/MPN	1 (5%)	2 (6%)		1 (5%)	3 (5%)		1 (5.9%)	2 (6.5%)		1 (4.8%)	3 (4.8%)		1 (5%)	3 (5.1%)		1 (5%)	3 (5%)	
	Aggressive lymphoma CR/PR	1 (5%)	1 (3%)		2 (10%)	4 (7%)		1 (5.9%)	1 (3.2%)		2 (9.5%)	5 (8.1%)		1 (5%)	3 (5.1%)		2 (10%)	6 (10%)	
	Aggressive lymphoma no CR/PR	2 (11%)	4 (11.1%)		2 (10%)	6 (10%)		2 (11.8%)	3 (9.7%)		2 (9.5%)	6 (9.7%)		1 (5%)	6 (10.2%)		2 (10%)	6 (10%)	
	Low grade lymphoma/ CLL	1 (5%)	2 (6%)		1 (5%)	3 (5%)		1 (5.9%)	2 (6.5%)		1 (4.8%)	3 (4.8%)		2 (10%)	3 (5.1%)		1 (5%)	3 (5%)	
Year Transplant	Median	2017	2015	**0.002**	2017	2015	**.003**	2017	2013	**.007**	2017	2014	**.014**	2017	2018	.58	2017	2014	**.0002**
DRI	Low	3 (16%)	2 (6%)	.74	4 (19%)	3 (5%)	.39	3 (18%)	1 (3%)	.48	4 (19%)	4 (6.5%)	.4	3 (15%)	3 (5.1%)	.58	4 (19%)	2 (3.3%)	.21
	Intermediate	8 (42%)	19 (53%)		8 (38%)	31 (53%)		8 (47.1%)	17 (54.8%)		8 (38.1%)	32 (51.6%)		8 (40%)	30 (50.8%)		8 (38.1%)	28 (45.9%)	
	High	4 (21%)	8 (22%)		4 (19%)	11 (19%)		4 (24%)	10 (32.3%)		4 (19%)	9 (14.5%)		4 (20%)	8 (13.6%)		4 (19%)	12 (19.7%)	
	Very high	1 (5%)	3 (8%)		1 (5%)	4 (7%)		1 (6%)	1 (3.2%)		1 (4.8%)	7 (11.3%)		1 (5%)	4 (6.8%)		1 (4.8%)	8 (13.1%)	
DRI not applicable	Prior AlloHCT	3 (16%)	4 (11%)		4 (19%)	10 (17%)		1 (6%)	2 (7%)		4 (19%)	10 (16%)		4 (20%)	14 (23.7%)		4 (19%)	11 (18%)	
KPS	70−80	10 (53%)	19 (53%)	.99	12 (57%)	32 (54%)	.82	9 (53%)	16 (52%)	.93	12 (57.1%)	34 (54.8%)	.85	11 (55%)	32 (54.2%)	.95	12 (57.1%)	34 (55.7%)	.91
	90−100	9 (47%)	17 (47%)		9 (43%)	27 (46%)		8 (47%)	15 (48%)		9 (43%)	28 (45%)		9 (45%)	27 (46%)		9 (43%)	27 (44%)	
HCT−CI	0	8 (42%)	13 (54%)	.57	8 (38%)	18 (60%)	.26	8 (47%)	12 (75%)	.13	8 (38.1%)	22 (56.4%)	.41	8 (40%)	18 (45%)	.43	8 (38.1%)	22 (68.8%)	.096
	1 or 2	4 (21%)			6 (29%)	7 (23%)		3 (18%)	3 (19%)		6 (29%)	8 (21%)			14 (35%)		6 (28.6%)	4 (12.5%)	

(*continued*)

Table 1 (*Continued*)

Donor comparator		CB			10/10 MUD PBSC			10/10 MUD BM			9/10 UD			Haplo			MSD		
		UM171 CB (n = 19)	CB (n = 36)	*P*	UM171 CB (n = 21)	MUD 10/10 PBSC (n = 59)	*P*	UM171 CB (n = 17)	MUD 10/10 BM (n = 31)	*P*	UM171 CB (n = 21)	UD 9/10 (n = 62)	*P*	UM171 CB (n = 20)	Haplo (n = 59)	*P*	UM171 CB (n = 21)	MSD (n = 61)	*P*
			6 (25%)											5 (25%)					
	≥ 3	7 (37%)	5 (21%)		7 (33%)	5 (17%)		6 (35%)	1 (6%)		7 (33%)	9 (23%)		7 (35%)	8 (20%)		7 (33.3%)	6 (18.8%)	
Weight (Kg)	median [IQR]	76 [69–83]	68 [61–76]	.052	78 [70–86]	73 [65–82]	.35	78 [72–84]	71.3 [63–79]	.14	78 [70–86]	80.5 [65–94]	.73	75.5 [68.8–84.5]	69 [56–76]	**.037**	78 [70–86]	75 [63–84]	.34
Conditioning	MAC	8 (42%)	17 (47%)		8 (38%)	24 (41%)	.84	8 (47%)	19 (61%)	.34	8 (38.1%)	27 (43.5%)	.66	8 (40%)	28 (47.5%)	.56	8 (38.1%)	32 (52.5%)	.26
	RIC	11 (58%)	19 (53%)	.72	13 (62%)	35 (59%)		9 (53%)	12 (39%)		13 (61.9%)	35 (56.5%)		12 (60%)	31 (52.5%)		13 (61.9%)	29 (47.5%)	
GVHD prophylaxis	CSA+MMF	7 (37%)	35 (97%)	< **.0001**	6 (29%)	19 (32%)	ND	6 (35%)	5 (16%)	ND	6 (28.6%)	17 (27.4%)	ND	7 (35%)	29 (49.2%)	.28	6 (29%)	16 (26%)	ND
	MMF+Tacro	12 (63%)	1 (3%)		15 (71%)	4 (7%)		11 (65%)	2 (7%)		15 (71%)	7 (11%)		13 (65%)	18 (30.5%)		15 (71%)	7 (12%)	
	CSA+MTX	0	0		0	34 (58%)		0	21 (68%)		0	25 (40%)		0	1 (2%)		0	25 (41%)	
	MTX+Tacro	0	0		0	2 (3%)		0	3(10%)		0	1 (2%)		0	0		0	1 (2%)	
	Other	0	0		0	0		0	0		0	12 (19%)		0	11 (19%)		0	12 (20%)	
Prior AlloHCT	Yes	3 (16%)	4 (11%)	.68	4 (19%)	10 (17%)	1	1 (6%)	2 (6.5%)	1	4 (19%)	10 (16%)	.74	4 (20%)	14 (24%)	1	4 (19%)	11 (18%)	1

10/10 MUD indicates 10/10 HLA-matched unrelated donor; 9/10 UD, 9/10 HLA-matched unrelated donor; ALL, acute lymphoblastic leukemia; AlloHCT, allogeneic hematopoietic cell transplant; AML, acute myeloid leukemia; BM, bone marrow; CB, cord blood; CLL, chronic lymphocytic leukemia; CR, complete remission; DRI, disease risk index[12]; CSA, cyclosporine; GVHD, graft versus host disease; Haplo, haploidentical donor; HCT-CI, hematopoietic cell transplantation-specific comorbidity index; IQR, interquartile range; KPS, Karnofsky performance status; MDS, myelodysplastic syndrome; MMF, mycophenolate mofetil; MPN, myeloproliferative neoplasm; MSD, matched sibling donor; MTX, methotrexate; ND, not done; PBSC, peripheral blood stem cells; PR, partial remission; Tacro, tacrolimus.

Comparisons were performed using the Chi-square or Fisher's exact test for categorical variables, and the Mann-Whitey U test for continuous variables. There were no significant differences between the groups except for year of transplant, median follow-up, weight of patient and GVHD prophylaxis.

Table 2
Engraftment. Engraftment outcomes following transplantation with UM171-expanded cord blood compared to 6 control groups from the EBMT registry.

		Graft Failure		Days to ANC > 500/μL	Days to platelets > 20 000/μL		
Group		Graft failure	Engrafted	Median [95% CI] *	Not achieved at last FU	Median [95% CI]†	Missing event
CB	**UM171 CB** (n = 19)	0	19	18 [12–20]	1	42 [36–49]	0
	CB (n = 36)	1	35	22 [17–32]	3	40 [25–52]	3
	***P*-value**			**.0009**		.41	
10/10 MUD PBSC	**UM171 CB** (n = 21)	0	21	18 [13–22.5]	1	42 [35–47]	0
	MUD PBSC (n = 59)	0	59	17 [14–21]	3	15 [12–20.5]	14
	***P*-value**			.94		<**.0001**	
10/10 MUD BM	**UM171 CB** (n = 17)	0	17	18 [13–22.5]	1	42.5 [35.2–49.5]	0
	MUD BM (n = 31)	2	29	23 [19.5–27.5]	1	20 [17.2–26.5]	9
	***P*-value**			**.014**		<**.0001**	
9/10 UD	**UM171 CB**(n = 21)	0	21	18 [13–22.5]	1	42 [35.2–47.7]	0
	9/10 UD (n = 61)	1	61	17 [14–21]	10	17 [12–25]	12
	***P*-value**			.98		<**.0001**	
Haplo	**UM171 CB** (n = 20)	0	20	18 [12–20]	1	42 [35–47]	0
	Haplo (n = 59)	4	55	19 [17–23]	7	26 [15–34]	11
	***P*-value**			.09		<**.0001**	
MSD	**UM171 CB** (n = 21)	0	21	18 [13–22.5]	1	42 [35.2–47.7]	0
	MSD (n = 61)	2	59	18 [15–21]	1	14 [11.25–16]	20
	***P*-value**			.83		<**.0001**	

10/10 MUD indicates 10/10 HLA-matched unrelated donor; 9/10 UD, 9/10 HLA-matched unrelated donor; ANC, absolute neutrophil count; BM, bone marrow; CB, cord blood; EBMT, European Society for Blood and Marrow Transplantation; FU, follow-up; Haplo, haploidentical donor; MSD, matched sibling donor; PBSC, peripheral blood stem cells.

* Only patients who achieved ANC > 500/μL.

† Only patients who achieved platelets > 20 000/μL.

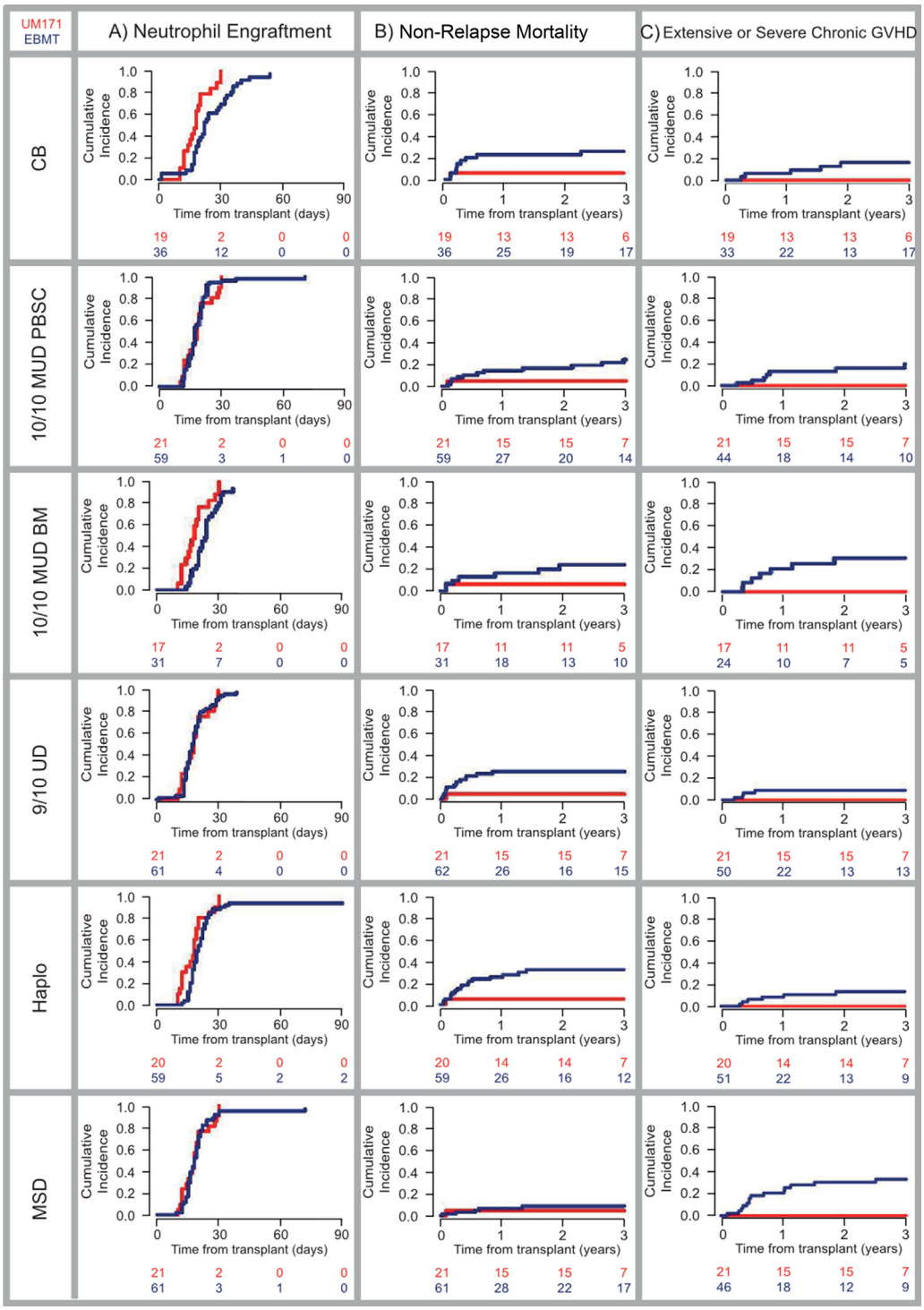

Figure 1. Neutrophil engraftment (A), non-relapse mortality (B), and extensive or severe chronic graft versus host disease (C). Cumulative incidences of neutrophil engraftment (A), non-relapse mortality (NRM, B), and extensive or severe chronic graft versus host disease (GVHD, C) of UM171 cord blood (CB) transplant recipients in red compared to the 6 control groups of the European Society for Blood and Marrow Transplantation (EBMT) registry in blue.

differences were observed between groups except for median year of transplant (2017 for UM171 versus 2015 for 10/10 PBSC MUD, Table 1). Median time to neutrophil engraftment was similar between groups, but platelet engraftment was delayed in the UM171 group at 42 days versus 15 days, although data were missing in half of the controls ($P < .0001$, Table 2). Severe or

Table 3
Clinical outcomes of UM171 cord blood compared to 6 other stem cell sources.

Outcomes	Time	N at risk UM171/ EBMT	UM171 cord blood	EBMT cohorts	HR (95% CI) UM171 versus EBMT	*P* value
Group = CB						
Acute GVHD II–IV	@ d180	19/35	63.2% [36.3–81.2]	54.3% [36.2–69.3]	1.01 (0.45–2.28)	.97
Acute GVHD III–IV	@ d180	19/35	10.5% [1.7-29.1]	17.1% [6.8–31.4]		.52
Chronic GVHD	@ 2yr	19/33	21.1% [6.2–41.9]	32.5% [16.5–49.6]	0.58 (0.17–1.9)	.37
Chronic GVHD (severe or extensive)*	@ 2yrs	19/33	0%	16.3% [5.7–31.7]		.07
Relapse	@ 2yrs	19/36	26.3% [9.2–47.4]	17.6% [6.9–32.2]	1.4 (0.4–4.92)	.6
NRM	@ 2yrs	19/36	5.3% [0.3–22]	22.2% [10.3–37]	0.22 (0.02–2.08)	.19
PFS	@ 2yrs	19/36	68.4% [42.8–84.4]	60.2% [42.1–74.3]	0.74 (0.29–1.91)	.53
OS	@ 2yrs	19/36	68.4% [42.8–84.4]	66.3% [48.3–79.3]	0.83 (0.32–2.15)	.7
GRFS	@ 1yr	19/35	62% [36.3-79.8]	57.1% [39.3–71.5]	0.55(0.23–1.31)	.18
	@ 2yrs		62% [36.3-79.8]	40.6% [23.9–56.7]		
Group = 10/10 MUD PBSC						
Acute GVHD II–IV	@ d180	21/55	71.4% [45.2–86.7]	41.8% [28.6–54.5]	1.59 (0.9–2.79)	.11
Acute GVHD III–IV	@ d180	21/55	10.5% [1.7-29.1]	16.4% [8–27.3]		.46
Chronic GVHD	@ 2yrs	21/47	23.8% [8.2–43.8]	35.8% [21.3–50.5]	0.5 (0.21–1.21)	.13
Chronic GVHD (severe or extensive)*	@ 2yrs	21/44	0%	16% [6.3–29.8]		**.04**
Relapse	@ 2yrs	21/59	23.8% [8.3–43.7]	33.1% [20.7–45.9]	0.6 (0.23–1.56)	.29
NRM	@ 2yrs	21/59	4.8% [0.3–20.2]	16.6% [8–27.9]	0.25 (0.03–2.47)	.24
PFS	@ 2yrs	21/59	71.4% [47.2–86]	50.3% [36.1–63]	0.49 (0.19–1.27)	.14
OS	@ 2yrs	21/59	71.4% [47.2–86]	54% [39.2–66.7]	0.51 (0.21–1.28)	.15
GRFS	@ 1yr	21/59	71.4% [47.2–86]	40.9% [27.7–53.6]	0.4 (0.17–0.95)	**.037**
	@ 2yrs		65.8% [41.2-2.82]	34.1% [21.6–47.1]		
Group = 10/10 MUD BM						
Acute GVHD II–IV	@ d180	17/30	64.7% [35.6–83.2]	26.7% [12.4–43.3]	2.87 (1.33–6.18)	**.007**
Acute GVHD III–IV	@ d180	17/30	11.8% [1.8-32]	10% [2.5–23.9]		.85
Chronic GVHD	@ 2yrs	17/25	17.6% [4–39.3]	40% [20.6–58.8]	0.36 (0.08–1.5)	.16
Chronic GVHD (severe or extensive)*	@ 2yrs	17/24	0%	30.6% [12.9–50.4]		**.015**
Relapse	@ 2yrs	17/31	29.4% [10.2–51.9]	23.5% [10.1–40.1]	1.21 (0.39–3.73)	.74
NRM	@ 2yrs	17/31	5.9% [0.3–24.2]	24% [10.2–40.9]	0.24 (0.03–1.65)	.15
PFS	@ 2yrs	17/31	64.7% [37.7–82.3]	52.5% [33.1–68.7]	0.72 (0.31–1.67)	.45
OS	@ 2yrs	17/31	64.7% [37.7–82.3]	59.1% [39.2–74.5]	0.81 (0.38–1.7)	.57
GRFS	@ 1yr	17/31	57.4% [30.6-77]	41.9% [24.7–58.3]	0.57 (0.27–1.21)	.14
	@ 2yrs		57.4% [32.5–77.8]	34.6% [18.5–51.3]		
Group = 9/10 UD						
Acute GVHD II–IV	@ d180	21/59	71.4% [45.2–86.7]	37.4% [25.1–49.6]	2.2 (1.18–4.11)	**.013**
Acute GVHD III–IV	@ d180	21/59	9.5% [1.5-26.7]	17% [8.7–27.7]		.41
Chronic GVHD	@ 2yrs	21/50	23.8% [8.2–43.8]	38.1% [24.1–51.9]	0.38 (0.13–1.1)	.075
Chronic GVHD (severe or extensive)*	@ 2yrs	21/50	0%	7.3% [2.3–16.2]		.21
Relapse	@ 2yrs	21/62	23.8% [8.3–43.7]	31.2% [19.6–43.6]	0.58 (0.18–1.81)	.35
NRM	@ 2yrs	21/61	4.8% [0.3–20.2]	25.4% [15–37.1]	0.16 (0.02–1.19)	.073
PFS	@ 2yrs	21/61	71.4% [47.2–86]	43.2% [30.1-55.6]	0.39 (0.14–1.07)	.068
OS	@ 2yrs	21/61	71.4% [47.2–86]	53.8% [39.7–65.9]	0.48 (0.18–1.3)	.15
GRFS	@ 1yr	21/61	65.8% [41.2-82]	38.4% [26.1–50.6]	0.4 (0.16–0.98)	**.046**

(*continued*)

Table 3 (*Continued*)

Outcomes	Time	N at risk UM171/ EBMT	UM171 cord blood	EBMT cohorts	HR (95% CI) UM171 versus EBMT	*P* value
	@ 2yrs		65.8% [41.2–82]	36.5% [24.3–48.7]		
Group = Haplo						
Acute GVHD II–IV	@ d180	20/56	65% [38.7–82.2]	30.4% [18.8–42.7]	2.3 (1.18-4.46)	**.014**
Acute GVHD III–IV	@ d180	20/56	5% [0.3-21.1]	8.9% [3.2–18.2]		.6
Chronic GVHD	@ 2yrs	20/52	20% [5.9–40.1]	28.9% [16.8–42.1]	0.52 (0.14–1.92)	.33
Chronic GVHD (severe or extensive)*	@ 2yrs	20/51	0%	12.5% [4.9–23.7]		.10
Relapse	@ 2yrs	20/59	25% [8.7–45.5]	27.4% [16.2–39.9]	0.74 (0.26–2.1)	.57
NRM	@ 2yrs	20/59	5% [0.3–21.1]	31.3% [19.2–44]	0.13 (0.02–1.06)	.056
PFS	@ 2yrs	20/59	70% [45.1–85.3]	41.3% [27.9–54.3]	0.42 (0.19–0.95)	**.038**
OS	@ 2yrs	20/59	70% [45.1–85.3]	44.3% [30.4–57.2]	0.41 (0.19–0.92)	**.03**
GRFS	@ 1yr	20/59	65% [40.3–81.5]	45.2% [31.9–57.7]	0.45 (0.2–1)	**.049**
	@ 2yrs		65% [40.3–81.5]	36.4% [23.6–49.3]		
Group = MSD						
Acute GVHD II–IV	@ d180	21/57	71.4% [45.2–86.7]	29.8% [18.5–42]	2.83 (1.54–5.21)	**.0008**
Acute GVHD III–IV	@ d180	21/57	9.5% [1.5-26.7]	15.8% [7.7–26.5]		.49
Chronic GVHD	@ 2yrs	21/49	23.8% [8.2–43.8]	41% [26.5–55]	0.46 (0.15–1.39)	.17
Chronic GVHD (severe or extensive)*	@ 2yrs	21/46	0%	26.9% [15.1–40]		**.01**
Relapse	@ 2yrs	21/61	23.8% [8.3–43.7]	41.9% [28.8–54.4]	0.49 (0.2–1.18)	.11
NRM	@ 2yrs	21/61	4.8% [0.3–20.2]	9.1% [3.3–18.7]	0.44 (0.11–1.77)	.25
PFS	@ 2yrs	21/61	71.4% [47.2–86]	49% [35.4–61.3]	0.48 (0.21–1.09)	.08
OS	@ 2yrs	21/61	71.4% [47.2–86]	56.5% [42.2–68.5]	0.57 (0.28–1.18)	.13
GRFS	@ 1yr	21/61	65.8% [41.2–82]	35.4% [23.2–47.9]	0.37 (0.16–0.82)	**.014**
	@ 2yrs		65.8% [41.2–82]	29.5% [18.1–41.8]		

10/10 MUD indicates 10/10 HLA-matched unrelated donor; 9/10 UD, 9/10 HLA-matched unrelated donor; ANC, absolute neutrophil count; BM, bone marrow; CB, cord blood; FU, follow-up; GRFS, graft-versus-host disease-free, relapse-free survival; GVHD, graft versus host disease; Haplo: haploidentical donor; MSD, matched sibling donor; NRM, non-relapse mortality; OS, overall survival; PBSC, peripheral blood stem cells; PFS, progression-free survival.

* *P*-value based on Gray test as Cox model (with cluster) cannot be used as there is no event in the UM171 CB group.Clinical outcomes, including acute and chronic graft versus host disease (GVHD), relapse rates, non-relapse mortality (NRM), progression-free survival (PFS), overall survival (OS) and GVHD-free, relapse-free survival (GRFS) of UM171-expanded cord blood recipients compared with matched cohorts from the EBMT registry. Comparisons between patients receiving UM171 CB and each other source of stem cells were performed using a Cox model. A cluster term was used to take into account the association within matching groups. Results were summarized using the hazard ratio (HR) and 95% confidence interval (CI). HR<1 favors UM171 CB for the criteria studied.

extensive chronic GVHD occurred significantly less frequently in UM171 patients (*P* = .04, Table 3, Figure 1C). Differences in NRM, RI, PFS, and OS were not statistically significant, though OS numerically favored UM171 patients (71% versus 54% at 2 years; Table 3 and Fig 2A). GRFS was superior at 2 years in the UM171 group at 66% versus 34% for controls (HR: 0.4, *P* = .037, Table 3 and Figure 2C).

UM171 CB Compared to BM From 10/10 MUD

Thirty-one controls were matched to 17 UM171 patients. Five UM171 patients could not be matched (4 patients had failed prior alloHCT). Patient characteristics are listed in Table 1, with no significant differences except for an earlier median year of transplant (2013 versus 2017) and longer follow-up for controls. The median time to neutrophil engraftment was shorter in the UM171 group (18 versus 23 d; Table 2 and Figure 1A). Platelet engraftment was faster in the MUD BM cohort (Table 2). Two graft failures occurred in the BM MUD group versus none with UM171 (Table 2). The UM171 CB patients experienced a higher incidence of grade II-IV acute GVHD; however, the incidence of severe (grade III-IV) acute GVHD was identical between groups (Table 3,

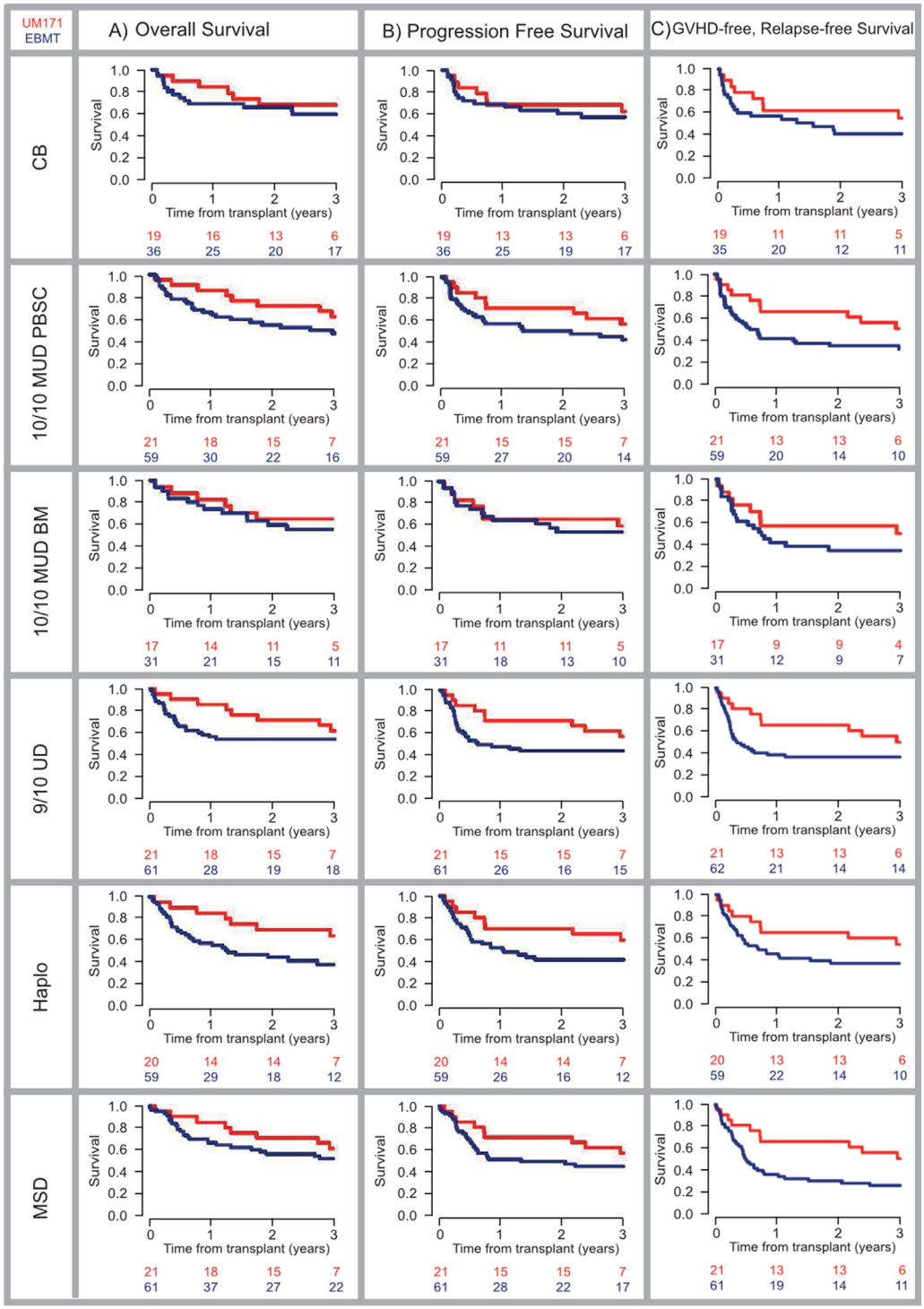

Figure 2. Overall survival (A), progression-free survival (B), GVHD-free, and relapse-free survival (C). Kaplan-Meier estimates of overall (A), progression-free (B), and GVHD-free, relapse-free (C) survival for UM171 cord blood (CB) transplants in red compared to 6 control groups from the European Society for Blood and Marrow Transplantation (EBMT) registry in blue.

Figure S1). Severe or extensive chronic GVHD at 2 yr was significantly higher in BM MUD recipients (31%) versus none for UM171 patients (P = .015, Table 3 and Figure 1C). NRM was numerically lower for UM171 (6% versus 24%; Table 3, Figure 1B), without statistical significance. PFS, OS, and relapse were similar. GRFS at 2 yr was numerically superior for UM171 (57% versus 35%, HR: 0.37; Table 3, Figure 2C), but it was not statistically significant.

UM171 CB Compared to 9/10 UD (PBSC and BM)

Sixty-two controls were matched to 21 UM171 CB patients. Patient characteristics are listed in Table 1 and no significant difference was noted between the 2 groups except for median year of transplant (2017 for UM171 CB versus 2014 for 9/10 UD). Time to neutrophil engraftment was similar (Table 2 and Figure 1A); however, platelet engraftment was significantly faster in the 9/10 UD cohort (Table 2). There was one graft failure amongst the controls. Grade II-IV acute GVHD incidence was higher for the UM171 patients, but grade III-IV acute GVHD incidence was similar (Table 3). NRM was numerically lower for UM171 CB (5%) compared to 9/10 UD (25%) recipients, without reaching statistical significance (P = .073, Table 3, Figure 1B). PFS was also numerically higher for UM171 CB (71% versus 43%, P = .068, Table 3, Figure 2B). However, UM171 CB patients had significantly superior GRFS at 2 yr (66% versus 37%, P = .046; Table 3, Figure 2C). Relapse and OS were not significantly different (Table 3).

UM171 CB Compared to Haplo Donor Grafts

The EBMT registry identified 59 controls for 20 UM171 patients. Amongst the 59 controls, 56 had received PTCy and 3 ATG. Patient characteristics (Table 1) did not differ significantly between the 2 groups except for higher patient weight, in the UM171 cohort (76 kg versus 69.0 kg). Median time to neutrophil engraftment was similar, but platelet engraftment was significantly faster in the haplo cohort (Table 2 and Figure 1A). However, only 85% of the haplo controls achieved platelet engraftment by d 100 as opposed to 95% for the UM171 patients. There were 4 graft failures in the haplo group but none in the UM171 group. The incidence of grade II-IV acute GVHD was higher for the UM171 patients but that of grade III-IV was no different (Table 3, Figure S1). The lower NRM of the UM171 group (5%) compared to the haplo controls (31%) was of borderline significance (P = .056, Table 3 and Figure 1B). Amongst the 56 patients having received PTCy, 15 died from NRM, indicating that the elevated NRM in the haplo group was not attributable to the ATG subgroup. PFS was significantly improved at 2 yr for UM171 patients (70% versus 41%, P = .038, Table 3, Figure 2B), translating into a superior OS at 2 yr for UM171 patients (70% versus 44%; P = .03; Table 3, Figure 2A). Finally, GRFS was higher for the UM171 patients at 2 yr (65% UM171 versus 36% haplo, P = .049, Table 3 and Figure 2C).

UM171 CB Compared to MSD (BM and PBSC)

Sixty-one controls were matched to 21 UM171 CB patients. There were no differences in patient characteristics (Table 1), except for a longer median follow-up for the MSD group, and the median year of transplant was 2014 for MSD controls and 2017 for UM171 cases. Median time to neutrophil engraftment was similar but platelet engraftment was faster in the MSD cohort (more than 50% data missing for platelets in the MSD group, Table 2, Figure 1A). Graft failure did not occur in the UM171 group, but there were 2 cases in the MSD group. Acute GVHD grade II-IV was higher for the UM171 patients but grade III-IV acute GVHD was similar (Table 3, Figure S1). Chronic extensive or severe GVHD was lower for UM171 patients (0%) compared to MSD controls (27%, P = .01, Table 3, Figure 1C). RI, NRM, PFS and OS were similar, however, GRFS was higher for the UM171 patients at 2 yr (66%) compared to MSD controls (30%, P = .014, Table 3 and Figure 2C).

DISCUSSION

This matched-pair analysis evaluated the short- and long-term outcomes of UM171-expanded CB transplantation versus 6 standard HSC donor types. UM171 CB transplants demonstrated prompt neutrophil recovery, faster than conventional CB and BM from 10/10 MUD and equivalent to other donor types. UM171 recipients experienced no moderate to severe chronic GVHD thus significantly lower compared to recipients of PBSC MUD, BM MUD, and MSD. Moreover, PFS and OS were significantly improved relative to haplo donor transplants. GRFS was consistently superior for UM171 CB compared to MUD PBSC, 9/10 UD, haplo, and MSD transplants.

The primary goal of the original phase I to II UM171 trial was to improve outcomes of CB transplantation by reducing its main disadvantage, the high NRM, stemming primarily from delayed engraftment and poor HLA matching [3]. The remarkably low NRM rate (4.5%) observed with UM171-expanded CB likely resulted from accelerated neutrophil engraftment, the absence of graft failure, robust immune reconstitution and the improved ability to select smaller, yet better HLA-matched units. Notably, over 80% of UM171 patients received $\geq$ 6/8 HLA-matched grafts, contrasting favorably against the predominantly 5/8 units historically used at our institution. Many UM171 patients received grafts considered too small for standard clinical use.

In this matched-pair analysis, NRM was numerically lower for the UM171 CB cohort at 5-6% compared to 9-31% for the other donor groups, but this difference did not reach statistical significance. Only the haplo group tended to have a higher NRM (of 31%) compared to that of the UM171 CB group. This lack of statistical significance likely stems from the small number of patients in the UM171 CB cohort, made even smaller by the inability to match all patients. Still, UM171 expanded CB achieved the critical goal of reducing NRM while preserving CB's advantages, as reflected by the absence of extensive/severe chronic GVHD.

Limitations of this study include its small UM171 patient cohort size, restricting statistical power and generalizability. High-risk diseases present in UM171 recipients further hindered matching controls as several patients could not be matched (eg, 1 patient had refractory relapsed ALL after a failed alloHCT). Additionally, incomplete data in the EBMT registry affected platelet recovery assessment, and the Hematopoietic Cell Transplantation-specific Comorbidity Index was unavailable for controls. Moreover, UM171 patients were enrolled prospectively and treated at only 2 centers, unlike the EBMT control cohorts, which were treated retrospectively across multiple centers. This difference introduces a potential selection bias that may have contributed to the lower NRM observed in the UM171 group, a limitation that cannot be fully adjusted for and should be considered when interpreting these results.

A similar matched-pair analysis was undertaken with the CIBMTR, but with only 2 control groups, conventional CB and 8/8 MUD PBSC transplants [14]. In that study, we were able to demonstrate more advantages for the UM171 CB group. NRM, PFS, GRFS and OS were improved for UM171-expanded CB compared with conventional CB recipients. Compared with 8/8 PBSC MUD controls, UM171 recipients had lower NRM, higher PFS and GRFS. Differences between European and American GVHD prophylaxis practices (eg, ATG use in Europe) likely contributed to variations between EBMT and CIBMTR results. Additionally, CIBMTR was able to identify controls more frequently and in greater numbers per UM171 patient, further influencing these differences.

Various techniques to augment the number of stem and progenitor cells have been reported. Omidubicel has been approved by the US Food and Drug Administration. Omidubicel studies have demonstrated very rapid neutrophil engraftment but no difference in long term outcomes [15]. Most patients in the Omidubicel trials received a 4/6 HLA-matched CB graft in contrast to the 80% of the UM171 CB patients who received a $\geq$ 6/8 HLA-matched CB transplant (which likely represents a better HLA match than a 4/6). This improved HLA matching contributed to the very low NRM observed in the UM171 CB patients. Nonetheless, the cost for cell expansion will need to be considered when selecting a graft.

In conclusion, our results suggest that UM171-expanded CB recipients have equivalent or improved short- and long-term outcomes compared to patients transplanted from other graft sources. Despite these promising results, the small number of patients in the UM171 CB cohort precludes any firm conclusions which should be addressed in subsequent larger clinical trials.

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Conflict of Interest Statement: S.C. has received consulting fees from ExCellThera. S.C., J.R., S.L., and G.S. are eligible to receive royalties if UM171 is commercialized. G.S. is a major stockholder and Chief Executive/Scientific Officer of ExCellThera. S. C. and J.R. have received funding for clinical trials from ExCellThera. ExCellThera holds the license for UM171. YC: has received institutional consulting fees for the advisory board from MSD, Novartis, Incyte, BMS, Pfizer, Abbvie, Roche, Jazz, Gilead, Amgen, Astra-Zeneca, Servier, Takeda, Pierre Fabre, Medac; and travel support from MSD,

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AI Disclosure: AI was used to spell-check the manuscript.

Authorship Statement: M.L. performed the statistical analysis reported herein. S.C. was responsible for study design, data collection, data analysis and interpretation and wrote the first draft as well as the final version of the manuscript. G.S. contributed to the writing of the first version of the manuscript as well as to study design. N.B. and I.A. contributed to data collection and review of the raw data. All the authors had access to the data and contributed to the review of the final data and to the manuscript.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2025.08.006.

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