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RESEARCH ARTICLE

Higher survival following transplantation with a mismatched unrelated donor with posttransplant cyclophosphamide-based graft-versus-host disease prophylaxis than with double unit umbilical cord blood in patients with acute myeloid leukemia in first complete remission: A study from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation

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Abstract

The best donor option for acute myeloid leukemia (AML) patients lacking an HLA-matched donor has remained intensively debated. We herein report the results of a large retrospective registry study comparing hematopoietic cell transplantation (HCT) outcomes between double-unit umbilical cord blood transplantation (dCBT, $n = 209$) versus 9/10 HLA-matched unrelated donor (UD) with posttransplant cyclophosphamide (PTCy)-based graft-versus-host disease (GVHD) prophylaxis (UD 9/10, $n = 270$) in patients with AML in first complete remission (CR1). Inclusion criteria consisted of adult patient, AML in CR1 at transplantation, either peripheral blood stem cells (PBSC) from UD 9/10 with PTCy as GVHD prophylaxis or dCBT without PTCy, transplantation between 2013 and 2021, and no in vivo T-cell depletion. The 180-day cumulative incidence of grade II-IV acute GVHD was 29% in UD 9/10 versus 44% in dCBT recipients ($p = .001$). After adjustment for covariates, dCBT recipients had a higher non-relapse mortality (HR = 2.35, 95% CI: 1.23–4.48; $p = .01$), comparable relapse incidence (HR = 1.12, 95% CI: 0.67–1.86; $p = .66$), lower leukemia-free survival (HR = 1.5, 95% CI: 1.01–2.23; $p = .047$), and lower overall survival (HR = 1.66, 95% CI: 1.08–2.55; $p = .02$) compared with patients receiving UD 9/10 HCT. In summary, our results suggest that transplantation outcomes are better with UD 9/10 with PTCy-based GVHD prophylaxis than with dCBT for AML patients in CR1. These data might support the use of UD 9/10 with PTCy-based GVHD prophylaxis over dCBT in AML patients lacking an HLA-matched donor.

1 | INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) has remained the best therapeutic option for fit patients with intermediate/high-risk acute myeloid leukemia (AML) in first complete remission (CR1).[1,2] The optimal donor for AML patients lacking an HLA-matched donor has remained intensively debated.[3–5] An important step has been accomplished with the BMT CTN 1101 trial which compared transplantation outcomes in patients randomized between human leukocyte antigen (HLA)-haploidentical bone marrow transplantation with posttransplant cyclophosphamide (PTCy)-based graft-versus-host disease (GVHD) prophylaxis versus double-unit unrelated umbilical cord blood transplantation (dCBT).[6] Although the trial was discontinued prematurely due to slow accrual and because the first primary endpoint (progression-free-survival [PFS]) was not met, the study demonstrated higher non-relapse mortality (NRM) and lower overall survival (OS) in patients randomized to the dCBT arm.

In the last two decades, PTCy has revolutionized HLA-haploidentical transplantation allowing prevention of both graft rejection and severe GVHD.[7] In addition, recent data have suggested that graft-versus-leukemia effects could be dissociated from GVHD following PTCy-based GVHD prophylaxis.[8–10] Outside of the HLA-haploidentical transplantation setting, recent data have shown that PTCy-based GVHD prophylaxis might improve transplantation outcomes in patients given grafts from HLA-mismatched unrelated donors in comparison to anti-thymocyte globulin (ATG)-based GVHD prophylaxis.[11]

Herein, we present the results of a large retrospective registry study ($n = 479$) comparing transplantation outcomes with dCBT versus 9/10 HLA-matched unrelated donors (UD 9/10) with PTCy-based GVHD prophylaxis in patients with AML in CR1. Our hypothesis was that transplantation outcomes following UD 9/10 PBSC transplantation with PTCy-based GVHD prophylaxis would result in at least comparable outcomes as those observed after dCBT in AML patients in CR1. We observed that indeed dCBT was associated with a higher incidence of acute GVHD and of NRM than UD 9/10, leading to lower OS and leukemia-free survival (LFS).

2 | PATIENTS AND METHODS

2.1 | Study design and inclusion criteria

We report the results of a retrospective, multicenter analysis using the dataset of the Acute Leukemia Working Party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT). The EBMT is a voluntary working group of more than 600 transplant centers that are required to report all consecutive stem cell transplantations and follow-ups once a year. The EBMT Med A/B standardized

data collection forms are submitted to the registry by transplant center personnel following written informed consent from patients in accordance with center ethical research guidelines. Accuracy of data is assured by the individual transplant centers and by quality control measures such as regular internal and external audits.

Inclusion criteria consisted of adult patient (defined as ≥18 years of age at transplantation), AML in CR1 at transplantation, either dCBT or peripheral blood stem cells (PBSC) from UD 9/10 with PTCy as GVHD prophylaxis, transplantation between 2013 and 2021, and no in vivo T-cell depletion.

2.2 | Ethics statement

The scientific board of the ALWP of the EBMT approved this research project. The study was conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines.

2.3 | Definitions

Reduced intensity conditioning (RIC) was defined as regimens combining fludarabine with either <6 Gy total body irradiation, ≤8 mg/kg busulfan, or with other nonmyeloablative drugs as previously reported.[12] Acute and chronic GVHD were graded according to previously reported criteria.[13] Comorbidities at transplantation were quantified using the hematopoietic cell transplantation-specific comorbidity-index (HCT-CI) score.[14] Cytogenetic risk was stratified using the MRC-UK classification, as previously reported.[15]

Relapse incidence was defined as the time to first documentation of active disease (i.e., presence of 5% bone marrow blasts and/or reappearance of the underlying disease) after transplantation.[16] NRM was defined as death without evidence of relapse or progression. OS was defined as the time from allo-HSCT to death, regardless of the cause. Events for LFS included relapse and death, whichever occurred first. Events for the composite endpoint GVHD-free and relapse-free survival (GRFS) included grade III-IV acute GVHD, severe chronic GVHD, relapse and death, whichever occurred first, as previously reported.[17]

2.4 | Statistical analyses

All patients meeting the inclusion criteria were included in the study. Start time was the day of allo-HSCT for all endpoints. Patients were censored at the time of last follow-up. The Kaplan–Meier method was used to estimate LFS, GRFS, and OS.[18]

Cumulative incidence functions were used to estimate relapse incidence and NRM in a competing risk setting. Relapse and death were treated as competing events for analyses assessing cumulative incidences of acute or chronic GVHD. For all comparisons of time to event endpoints, patients were censored at 2 years posttransplant in order to take into account for the different follow-up between the two groups.

A comparison of outcomes between the two groups was performed using Cox models. Factors included in the model consisted of patient age, year of transplantation, secondary versus de novo AML, adverse cytogenetics or not, time from diagnosis to transplantation, conditioning intensity, patient CMV serostatus, Karnofsky performance score, and HCT-CI score. For conditioning intensity, we performed Cox models adjusted either for the RIC versus myeloablative conditioning (MAC) classification,[12] or for the transplant conditioning intensity (TCI) score.[19,20] Further, in order to take into account the heterogeneity in the effect of a characteristic or a treatment across centers, we introduced a random effect (also named frailty effect) in Cox multivariate models.[21] Then, the same random effect was shared by all patients within the same center. Results were expressed as the hazard ratio (HR) with the 95% confidence interval (95% CI). All tests were two-sided with the type I error rate fixed at 0.05 for the determination of factors associated with time-to-event outcomes. Statistical analyses were performed with SPSS 25.0 (SPSS Inc, Chicago, IL, USA), R 4.0.1 (R Core Team, 2019), R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/).

3 | RESULTS

3.1 | Patients

A total of 479 patients met the inclusion criteria, comprising 270 UD 9/10 recipients and 209 dCBT recipients. Median patient age was 55 years old (interquartile range [IQR], 43–63 years) and was comparable between both groups (Table 1). Median year of transplantation was 2019 for UD 9/10 patients versus 2016 for dCBT recipients ($p < .001$). In comparison with dCBT patients, UD 9/10 recipients had a longer time from diagnosis to allo-HSCT (median 5.4 months vs. 5.1 months, $p = .02$), more frequently received a MAC (51% vs. 21%, $p < .0001$), more frequently had a Karnofsky Performance Scale (KPS) score ≥90 (82% vs. 73%, $p = .034$), and were more frequently cytomegalovirus (CMV) seropositive (73% vs. 61%, $p = .006$). TCI scores tended to be more frequently lower in dCBT than in UD 9/10 patients.[19,20] Among UD 9/10 recipients, the numbers of patients with the HLA-mismatch at the HLA-A, -B, -C, -DR, and -DQ loci were 107, 54, 44, 25, and 40, respectively. GVHD prophylaxis was most often carried out with a combination of a calcineurin inhibitor and mycophenolate mofetil in both arms.

3.2 | Engraftment and graft-versus-host disease

Neutrophil engraftment was significantly faster in UD 9/10 than in dCBT patients with a median time of 19 (IQR:17–23) versus 25 (IQR: 18–34) days, respectively ($p < .0001$) (Figure 1A). In addition, 1.5% of UD 9/10 versus 3.3% of dCBT recipients failed to achieve neutrophil engraftment at Day 60.

The 180-day cumulative incidences of grade II-IV and grade III-IV acute GVHD were 29.2% and 10%, respectively, in UD 9/10 recipients, versus 44.4% ($p = .001$) and 15.5% ($p = .07$), respectively, in

TABLE 1 Patient characteristics according to donor type.

		UD9/10 ($n = 270$)	dCBT ($n = 209$)	p
Follow-up (mo)	Median [IQR]	24.9 [24.0–29.9]	57.6 [44.3–66.3]	<.001
Patient age (years)	Median (min–max) [IQR]	54.9 (19–74.2) [44.7–63.9]	55.6 (19.4–73.2) [40.9–62.5]	.32
Secondary AML	De novo	220 (81.5%)	166 (79.4%)	.57
	secAML	50 (18.5%)	43 (20.6%)	
Cytogenetics	Favorable	13 (5.6%)	5 (3.2%)	.034
	Intermediate	169 (72.2%)	100 (63.3%)	
	Adverse	52 (22.2%)	53 (33.5%)	
	Missing	36	51	
	Not adverse	218 (80.7%)	156 (74.6%)	.11
	Adverse	52 (19.3%)	53 (25.4%)	
FLT3	FLT3-wt	85 (57.8%)	66 (62.9%)	.42
	FLT3-ITD	62 (42.2%)	39 (37.1%)	
	Missing	123	104	
NPM1	NPM1 unmutated	86 (64.2%)	71 (67.6%)	.58
	NPM1 mutated	48 (35.8%)	34 (32.4%)	
	Missing	136	104	
Year of transplant	Median (min–max)	2019 (2013–2021)	2016 (2013–2021)	<.0001
Time, diagnosis to HSCT (mo)	Median (min–max) [IQR]	5.4 (2–21.5) [4.4–6.9]	5.1 (2–21.7) [3.9–6.5]	.02
MRD pre-HSCT	MRD neg	71 (57.7%)	49 (74.2%)	.025
	MRD pos	52 (42.3%)	17 (25.8%)	
	Missing	147	143	
Patient sex	Male	151 (55.9%)	108 (51.7%)	.35
	Female	119 (44.1%)	101 (48.3%)	
Donor sex	Male	183 (68%)	93 (47.7%)	<.0001
	Female	86 (32%)	102 (52.3%)	
	Missing	1	14	
Female to male combination	No F → M	228 (84.8%)	149 (73.4%)	.002
	F → M	41 (15.2%)	54 (26.6%)	
	Missing	1	6	
Conditioning regimen	BuFlu	113 (41.9%)	0 (0%)	
	TBF	58 (21.5%)	8 (3.8%)	
	FluMel	18 (6.7%)	0 (0%)	
	FluTreo	27 (10%)	0 (0%)	
	Cy-TBI	0 (0%)	2 (1%)	
	Flu-TBI	36 (13.3%)	193 (92.3%)	
	Other CT	18 (6.7%)	6 (2.9%)	
Conditioning intensity	MAC	137 (50.7%)	43 (20.6%)	<.0001
	RIC	133 (49.3%)	166 (79.4%)	
TCI	[1, 2]	98 (39.4%)	94 (47%)	.056
	[2.5–3.5]	125 (50.2%)	78 (39%)	
	[4–6]	26 (10.4%)	28 (14%)	
	Missing	21	9	
Karnofsky score	<90	48 (18.5%)	51 (26.8%)	.034
	≥90	212 (81.5%)	139 (73.2%)	
	Missing	10	19	

(Continues)

TABLE 1 (Continued)

		UD9/10 ($n = 270$)	dCBT ($n = 209$)	p
HCT-CI	HCT-CI = 0	143 (54.4%)	73 (44.5%)	.13
	HCT-CI = 1 or 2	51 (19.4%)	41 (25%)	
	HCT-CI ≥ 3	69 (26.2%)	50 (30.5%)	
	Missing	7	45	
Patient CMV	Pat. CMV neg	71 (26.8%)	80 (38.6%)	.006
	Pat. CMV pos	194 (73.2%)	127 (61.4%)	
	Missing	5	2	
Cells infused	TNC (108/kg) median [IQR]	8.1 [6.04–10.68]	0.46 [0.35–0.60]	
	CD34 (106/kg) median [IQR]	6.34 [5.12–8.78]	0.11 [0.05–0.26]	
GVHD prophylaxis	CSA or Tacro	49 (18.1%)	5 (2.4%)	
	CSA + MTX	2 (0.7%)	3 (1.4%)	
	CSA + MMF or Tacro+MMF	190 (70.3%)	195 (93.3%)	
	MMF + Siro	15 (5.6%)	0 (0%)	
	Other	14 (5.2%)	6 (2.9%)	

Abbreviations: BuFlu, busulfan + fludarabine; CMV, cytomegalovirus; CSA, cyclosporine; Cy-TBI, cyclophosphamide + total body irradiation; dCBT, double umbilical cord blood transplantation; F → M, female donor to male recipient; FLT3-ITD, FMS-like tyrosine kinase 3 internal tandem duplication; FLT3-wt, FMS-like tyrosine kinase 3 wild-type; FluMel, fludarabine + melphalan; Flu-TBI, fludarabine + total body irradiation ± other drugs; FluTreo, fludarabine + treosulfan; HCT-CI, hematopoietic cell transplant-specific comorbidity index[14]; IQR, interquartile range; MAC, myeloablative conditioning; max, maximum; min, minimum; MMF mycophenolate mofetil; mo, months; MRD, minimal residual disease; MTX, methotrexate; neg, negative; NPM1, nucleophosmin; Pat., patient; pos, positive; RIC, reduced intensity conditioning; secAML, secondary acute myeloid leukemia; SIRO, sirolimus; Tacro, tacrolimus; TBF, thiotepa + busulfan + fludarabine; TCI, transplant conditioning intensity[19,20]; TNC, total nucleated cells; UD 9/10, 9/10 HLA-matched unrelated donor.

dCBT recipients (Figure 1B,C). Grade IV acute GVHD occurred in six UD 9/10 patients (2.3%) versus 10 dCBT patients (4.9%). On multivariate analysis, dCBT patients had a higher incidence of grade II-IV acute GVHD than UD 9/10 patients (HR = 1.61, 95% CI: 1.04–2.51, $p = .034$).

The 2-year cumulative incidence of chronic and extensive chronic GVHD were 28.5% and 12.9%, respectively, in UD 9/10 patients, versus 28.1% ($p = .87$) and 7.8% ($p = .11$), respectively, in dCBT recipients (Figure 1D). No difference in the incidence of chronic GVHD between dCBT and UD 9/10 patients (HR = 0.9, 95% CI: 0.5–1.59, $p = .71$) was observed in multivariable analysis.

3.3 | Relapse and non-relapse mortality

The 2-year cumulative incidence of relapse was 23.5% in UD 9/10 versus 27% in dCBT recipients ($p = .39$) (Figure 2). On multivariate analysis, dCBT and UD 9/10 recipients had comparable risks of relapse (HR = 1.12, 95% CI: 0.67–1.86; $p = .66$) while adverse cytogenetics was associated with a higher risk of relapse (HR = 1.71, 95% CI: 1.09–2.7; $p = .02$) compared with no adverse cytogenetics (Table 2A). Comparable findings were observed when the multivariate models were adjusted for TCI instead of for RIC versus MAC conditioning (Table 2B).

The 2-year cumulative incidence of NRM was 12.5% in UD 9/10 versus 18% in dCBT recipients ($p = .07$) (Figure 2). On multivariate analysis, dCBT recipients had a higher NRM than UD 9/10 recipients (HR = 2.35, 95% CI: 1.23–4.48; $p = .01$) while NRM also increased with older patient age at transplantation (HR per 10 years = 1.28, 95% CI: 1.0–1.65; $p = .053$) (Table 2A).

3.4 | GVHD-free and relapse-free survival, leukemia-free survival, and overall survival

Two-year GRFS was 51% in UD 9/10 patients versus 46% ($p = .11$) in dCBT recipients. On multivariate analysis, no variables were significantly associated with GRFS. Two-year LFS was 64% in UD 9/10 patients versus 55% ($p = .028$) in dCBT recipients (Figure 2). Further, dCBT (HR = 1.5, 95% CI: 1.01–2.23; $p = .047$) and older age (HR per 10 years =1.19, 95% CI: 1.02–1.38; $p = .029$) were associated with lower LFS (Table 2A).

Two-year OS was 70% in UD 9/10 patients versus 60% ($p = .016$) in dCBT recipients (Figure 2). On multivariate analysis, dCBT (HR = 1.66, 95% CI: 1.08–2.55; $p = .02$) and older age (HR per 10 years =1.27, 95% CI: 1.07–1.5; $p = .006$) were associated with lower OS (Table 2A). Comparable findings were observed when the multivariate models were adjusted for TCI instead of for RIC versus MAC conditioning (Table 2B). With respect to cause of death, dCBT patients died more frequently from infection, and from GVHD than UD 9/10 patients (Table 3).

4 | DISCUSSION

The BMT-CTN 1101 trial has shown that HLA-haploidentical bone marrow transplantation could be a better transplantation option than dCBT.[6] However, using real-life data, our group observed comparable outcomes in patients given dCBT or PBSC from HLA-haploidentical donors, with PTCy.[22] A recent study showed that PTCy might

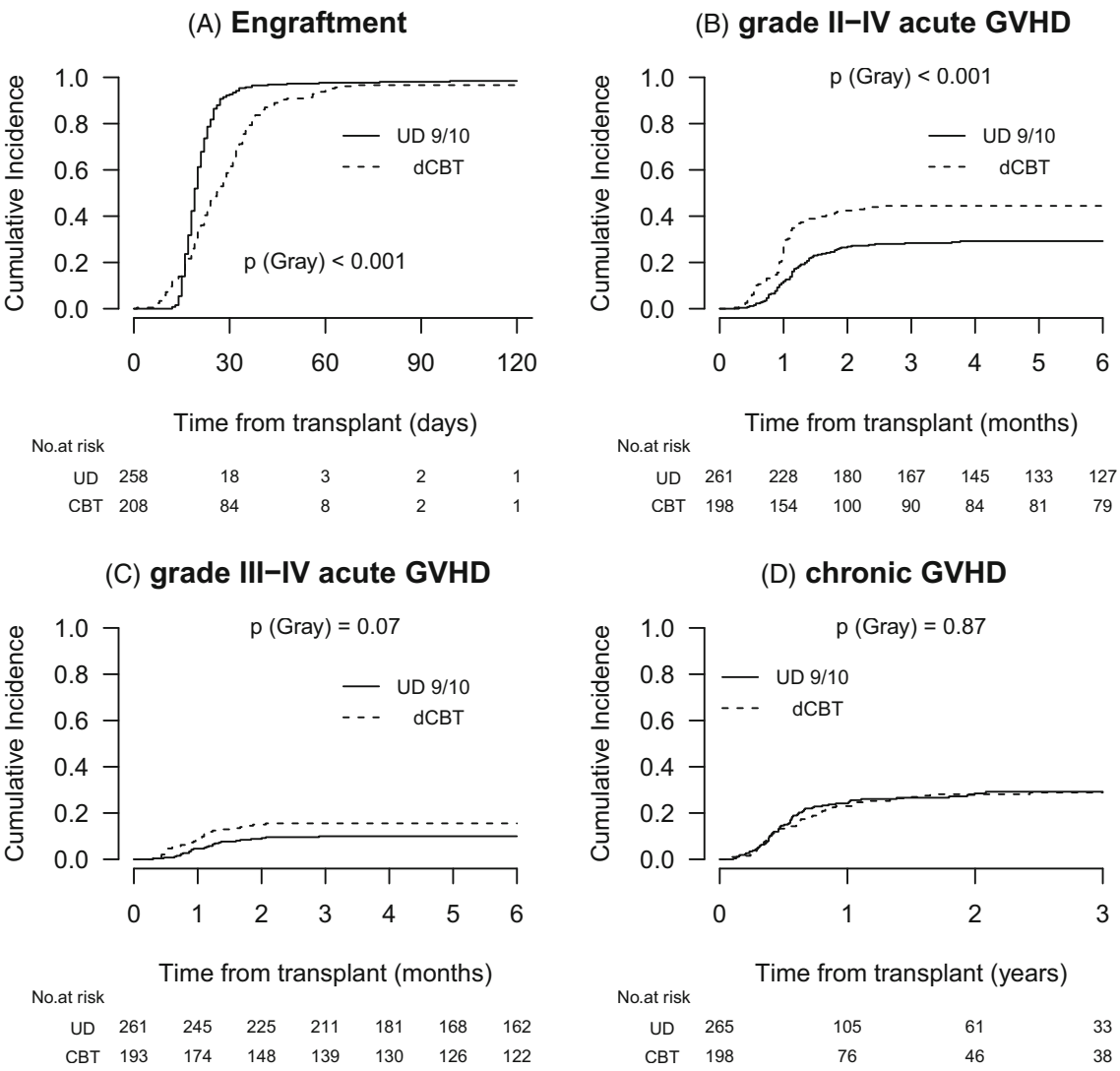

FIGURE 1 Engraftment and graft-versus-host disease (GVHD). (A) Cumulative incidence of neutrophil engraftment. (B) Cumulative incidence of Grades II–IV acute GVHD. (C) Cumulative incidence of Grades III–IV acute GVHD. (D) Cumulative incidence of chronic GVHD.

improve transplantation outcomes in comparison to ATG in patients given grafts from UD 9/10[11] while other retrospective studies have observed better transplantation outcomes in AML patients given grafts from UD 9/10 with PTCy-based GVHD prophylaxis as those given grafts from HLA-haploidentical donors.[23,24] These data prompted us to perform a study comparing transplantation outcomes between UD 9/10 with PTCy versus dCBT in a homogenous population of AML in CR1 not given in vivo T cell depletion. Several observations were made.

Firstly, transplants from UD 9/10 with PTCy were associated with low incidences of grade II-IV and grade III-IV acute GVHD (29% and 10%, respectively). Indeed, in comparison to dCBT recipients, UD 9/10 PTCy patients had a lower incidence of grade II-IV acute GVHD while a similar trend was observed for grade III-IV acute GVHD. These results illustrate the efficiency of PTCy at preventing GVHD in the HLA-mismatched setting, as well as the higher incidence of acute GVHD associated with dCBT in comparison to single-unit CBT.[22,25] The incidence of chronic GVHD was comparable and relatively low in both groups, with perhaps a suggestion of a slightly higher incidence of extensive chronic GVHD in UD 9/10 patients. It should be noted that the use of ATG was an exclusion criterion in our study, as in the BNT BMT-CTN 1101 trial, which might have contributed to the high incidence of acute GVHD in the CBT group. Indeed, prior studies have reported lower incidence of acute GVHD but higher NRM and lower OS with the use of ATG in the CBT setting.[26,27] However, this could be due to the administration of too high a dose of ATG, since encouraging transplantation outcomes and good immune reconstitution were observed with individualized dosing of ATG in pediatric CBT recipients.[28] In addition, intensifying MMF dosing has been shown to reduce acute GVHD after dCBT.[29]

A second observation was that the incidence of relapse was identical (and relatively low) in the two groups of patients. The low incidence of relapse combined with the low incidence of GVHD in UD 9/10 patients could be an illustration of the separation of graft-versus-leukemia effects from GVHD following PTCy-based GVHD

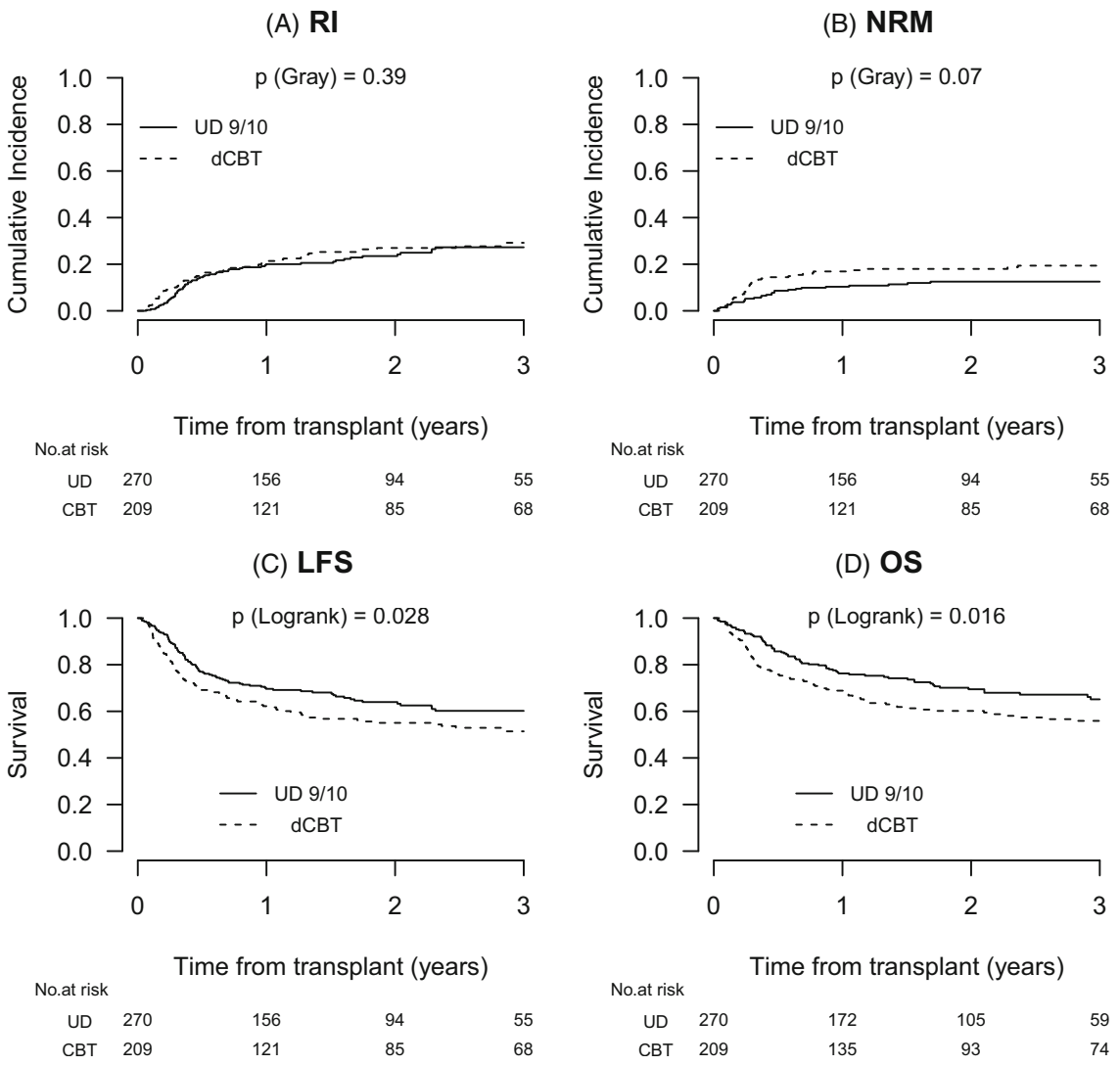

FIGURE 2 Transplantation outcomes. (A) Cumulative incidence of relapse (RI). (B) Cumulative incidence of non-relapse mortality (NRM). (C) Leukemia-free survival (LFS). (D) Overall survival (OS).

prophylaxis, as previously suggested.[8–10] The low incidence of relapse in dCBT recipients is also in line with prior publications suggesting that this approach is associated with high graft-versus-leukemia effects.[30–34]

A third observation was that dCBT patients had a higher NRM leading to lower LFS and OS. This observation confirms prior observations from our group in a study comparing transplantation outcomes of AML patients (in CR1, CR2, or with advanced AML) receiving PBSCs or bone marrow from UD 9/10 versus single-unit or dCBT, with or without in vivo T-cell depletion.[35] Looking at the cause of death, deaths from infection and from GVHD were more frequent in dCBT patients. These observations are in concordance with those made in the BMT CTN 1101 trial in which deaths from infection were more frequent in dCBT patients than in patients given bone marrow from HLA-haploidentical donors.[6] In addition, transplant-associated costs need to be taken into consideration given the high costs associated with dCBT.[36,37] It should be noted, however, that recent progress in the field of ex vivo cord blood expansion has allowed a decrease in the incidence of NRM after CBT.[38,39] Randomized studies comparing UD 9/10 with PTCy versus expanded CBT are needed to define the best donor option for patients lacking an HLA-matched donor, although it is unlikely that a prospective randomized phase III trial will address this question in the near future. Another important question that remains to be solved in prospective randomized studies is whether in the PTCy-based GVHD prophylaxis setting, UD 9/10 transplants result in better transplantation outcomes than HLA-haploidentical transplantation. Indeed, in the PTCy-based GVHD prophylaxis setting, a prior study from our group observed better LFS and OS with UD 9/10 than with HLA-haploidentical transplantation in AML patients in CR at transplantation.[24] Furthermore, a similar trend for better transplantation outcome with UD 9/10 was observed in a cohort of AML patients with active disease at transplantation.[23]

The number of UD 9/10 recipients in our study was too low to assess the impact of the HLA-mismatched locus on transplantation

TABLE 2 Multivariate Cox model results. (A) With conditioning intensity defined with reduced intensity conditioning versus myeloablative conditioning classification. (B) With conditioning intensity defined with the transplant conditioning intensity classification.

	RELAPSE		NRM		LFS		OS	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
A								
DCBT versus UD 9/10	1.12 (0.67–1.86)	.66	2.35 (1.23–4.48)	**.01**	1.5 (1.01–2.23)	**.047**	1.66 (1.08–2.55)	**.02**
Age (per 10 years)	1.12 (0.93–1.36)	.23	1.28 (1–1.65)	.053	1.19 (1.02–1.38)	**.029**	1.27 (1.07–1.5)	**.006**
Year of HCT	0.99 (0.89–1.1)	.87	1.06 (0.93–1.2)	.39	1.02 (0.94–1.1)	.69	1.04 (0.95–1.13)	.43
secAML versus de novo	1.12 (0.67–1.88)	.66	0.83 (0.43–1.63)	.59	1 (0.66–1.5)	.99	0.84 (0.53–1.33)	.46
Adverse cytogenetics	1.71 (1.09–2.7)	**.02**	0.77 (0.4–1.49)	.44	1.28 (0.88–1.85)	.19	1.13 (0.75–1.7)	.56
Time diagnosis to HSCT (mo)	1.02 (0.94–1.09)	.69	0.99 (0.89–1.09)	.77	1 (0.95–1.06)	.92	1.01 (0.95–1.07)	.74
RIC versus MAC	1.08 (0.62–1.87)	.78	0.82 (0.4–1.66)	.58	0.97 (0.63–1.5)	.89	1.02 (0.63–1.65)	.94
Pat. CMV pos	1.37 (0.86–2.2)	.19	1.42 (0.78–2.58)	.26	1.39 (0.96–2.01)	.083	1.4 (0.93–2.1)	.1
KPS ≥ 90	0.89 (0.54–1.47)	.65	0.64 (0.36–1.14)	.13	0.78 (0.54–1.14)	.2	0.75 (0.5–1.12)	.16
HCT-CI = 0 (reference)	1		1		1		1	
HCT-CI = 1 or 2	1.14 (0.67–1.95)	.62	0.74 (0.35–1.57)	.44	0.97 (0.63–1.5)	.9	0.78 (0.48–1.27)	.32
HCT-CI ≥ 3	1.22 (0.74–2.02)	.44	1.68 (0.94–3.02)	.082	1.4 (0.96–2.05)	.083	1.27 (0.84–1.91)	.25
Centre (frailty)		.93		.93		.73		.74
B								
dCBT versus UD 9/10	1.14 (0.69–1.88)	.62	2.15 (1.15–4)	**.016**	1.47 (0.95–2.27)	.084	1.63 (1.07–2.5)	**.024**
Age (per 10 years)	1.08 (0.9–1.3)	.42	1.22 (0.96–1.55)	.1	1.13 (0.97–1.31)	.11	1.22 (1.04–1.44)	**.018**
Year of HSCT	1 (0.9–1.11)	.97	1.06 (0.93–1.21)	.38	1.02 (0.94–1.11)	.6	1.04 (0.95–1.14)	.44
secAML versus de novo	1.1 (0.63–1.9)	.74	0.83 (0.41–1.67)	.6	0.97 (0.62–1.51)	.89	0.85 (0.52–1.37)	.5
Adverse cytogenetics	1.8 (1.14–2.86)	**.012**	0.64 (0.32–1.28)	.21	1.25 (0.85–1.83)	.26	1.08 (0.71–1.64)	.71
Time diagnosis to HSCT (months)	1.02 (0.95–1.11)	.56	0.99 (0.9–1.09)	.88	1.01 (0.95–1.08)	.65	1.02 (0.96–1.08)	.58
TCI [1, 2] reference	1		1		1		1	
[2.5–3.5]	0.8 (0.49–1.3)	.36	1.27 (0.72–2.24)	.41	0.96 (0.64–1.45)	.84	0.95 (0.64–1.41)	.8
[4–6]	0.65 (0.27–1.55)	.33	0.65 (0.18–2.35)	.51	0.6 (0.28–1.3)	.2	0.6 (0.26–1.39)	.23
Pat. CMV pos	1.46 (0.89–2.39)	.13	1.43 (0.77–2.63)	.26	1.41 (0.95–2.09)	.086	1.5 (0.98–2.29)	.064
KPS ≥ 90	0.81 (0.48–1.35)	.42	0.67 (0.37–1.22)	.19	0.69 (0.46–1.04)	.08	0.73 (0.48–1.11)	.14
HCT-CI = 0 (reference)	1		1		1		1	
HCTCI = 1 or 2	1.05 (0.59–1.85)	.87	0.78 (0.37–1.65)	.52	0.95 (0.6–1.51)	.83	0.77 (0.46–1.27)	.3
HTCI ≥ 3	1.23 (0.73–2.06)	.44	1.49 (0.82–2.71)	.19	1.41 (0.94–2.12)	.096	1.21 (0.79–1.84)	.38
Centre (frailty)		.24		.93		.2		.23

Note: Bold values are $P < .05$.

Abbreviations: CMV, cytomegalovirus; dCBT, double umbilical cord blood transplantation; HCT-CI, hematopoietic cell transplant-specific comorbidity index; KPS, Karnofsky performance score; LFS, leukemia-free survival; MAC, myeloablative conditioning; mo, months; NRM, non-relapse mortality; OS, overall survival; pat., patient; pos, positive; RIC, reduced intensity conditioning[12]; TCI, transplant conditioning intensity[19,20]; UD 9/10, 9/10 HLA-matched unrelated donor.

outcome. However, a recent study in patients with various hematological malignancies, from the EBMT Cellular Therapy and Immunobiology Working Party, suggested that HLA-mismatch at HLA-A and HLA-B loci remained associated with a lower OS in patients given PTCy-based GVHD prophylaxis.[40]

Our study has limitations including its retrospective registry-based design, the lack of data on the mutational AML landscape and minimal residual disease in a high proportion of patients, the missing data on PTCy dosing and schedule of administration and on transplant-associated costs, and some imbalances between the groups. However, these imbalances were adjusted for in the multivariate Cox models. The strengths of the study are the relatively high number of patients in each group and their relative uniformity (single disease, all patients in CR1 at transplantation, uniform use of PBSCs in the 9/10 PTCy group, and uniform dCBT in the cord blood group).

In summary, our results suggest that transplantation outcomes are better with UD 9/10 with PTCy-based GVHD prophylaxis than with dCBT for AML patients in CR1. Current data combined with prior observations from our group showing at least comparable outcomes with UD 9/10 with PTCy-based GVHD prophylaxis compared with

TABLE 3 Cause of death.

	UD 9/10 ($n = 79$)	dCBT ($n = 91$)
Original disease	47 (60.3%)	47 (54%)
Infection	13 (16.7%)	21 (24.1%)
GVHD	7 (9%)	12 (13.8%)
Cardiac toxicity	1 (1.3%)	0 (0%)
Hemorrhage	1 (1.3%)	1 (1.1%)
VOD	1 (1.3%)	0 (0%)
Second malignancy	1 (1.3%)	2 (2.3%)
MOF	3 (3.8%)	0 (0%)
CNS toxicity	1 (1.3%)	0 (0%)
Other HCT related	1 (1.3%)	1 (1.1%)
Non-HCT related	2 (2.6%)	3 (3.4%)
Missing	1	4

Abbreviations: CNS, central nervous system; dCBT, double umbilical cord blood transplantation; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; MOF, multiple organ failure; UD 9/10, 9/10 HLA-matched unrelated donor; VOD, veno-occlusive disease of the liver.

HLA-haploidentical transplantation[23,24] might support the use of UD 9/10 with PTCy-based GVHD prophylaxis in patients without HLA-matched donors.

AUTHOR CONTRIBUTIONS

FB wrote the manuscript, designed the study, and interpreted the data. ML designed the study, performed the statistical analyses, interpreted the data, and edited the manuscript. FC and MM designed the study, interpreted the data, and edited the manuscript. JVe, JVy, PvdB, EM, DB, RP, AK, CEB, MR, PC, EF, JB, JS, and AR reviewed the manuscript and provided clinical data. All authors approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

FB has received travel grants and/or speaker honoraria from Pfizer, Celgene, Abbvie, Novartis, and Sanofi. JV has received speaker honoraria from AbbVie and ExCellThera. The other authors declare that they have no relevant conflict of interest.

DATA AVAILABILITY STATEMENT

ML and MM had full access to all the data in the study. Data are available upon reasonable request. Please contact Dr. Myriam Labopin (myriam.labopin@upmc.fr).

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