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Comparison of long-term outcome for AML patients alive free of disease 2 years after allogeneic hematopoietic cell transplantation with umbilical cord blood versus unrelated donor: a study from the ALWP of the EBMT

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Since cord blood transplantation (CBT) has been associated with high graft-versus-leukemia effects and a low incidence of chronic graft-versus-host disease (GVHD), we hypothesized that long-term outcomes might be better in CBT patients than in those given grafts from unrelated donors (UD). Therefore, we performed a landmark study comparing long-term outcomes in acute myeloid leukemia (AML) patients alive and disease-free 2 years after transplantation who received grafts from either CBT or UD. A total of 364 CBT recipients, 2648 UD 10/10 patients and 681 patients given grafts from UD 9/10 were included. Median follow-up was 6.0 years. Five-year leukemia-free survival (LFS) from transplantation was 86% in CBT patients, 84% in UD 10/10 patients ($P = 0.36$) and 84% in UD 9/10 patients ($P = 0.86$). On multivariate analysis, donor type had no impact on LFS. Similarly, no impact of donor type was observed on relapse incidence or non-relapse mortality. Factors associated with poorer LFS on multivariate analysis included higher age at transplantation ($P < 0.001$), male gender ($P < 0.001$), second complete remission (CR2) versus CR1 ($P = 0.05$), secondary AML ($P = 0.01$), antecedent of chronic GVHD ($P < 0.001$) and poor-risk cytogenetics ($P = 0.01$). In conclusion, our study shows that long-term outcome for AML patients in CR two years after transplantation is not impacted by donor type.

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INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HCT) has remained the best curative option for patients with poor or intermediate-risk AML in first complete remission (CR) as well as for AML patients in second CR (CR2) [1–5]. For patients who lack a fit HLA-identical sibling donor, transplantation with either an HLA-matched or HLA-mismatched unrelated donor (UD), HLA-haploidentical or umbilical cord blood (CB) donor has remained an adequate option.

Many studies comparing the impact of an alternative stem cell source on transplantation outcomes have been reported with a relatively short follow-up [6–8]. This is unfortunate since prior studies have demonstrated that allo-HCT recipients are at higher risk of mortality than the normal population [9]. Furthermore, a recent report from our group underlined that up to 38% of AML patients alive in CR, 2 years after UD transplantation relapsed and or died in the following 8 years [10].

Although CB transplantation (CBT) has been associated with delayed engraftment and early non-relapse mortality (NRM), it also has been associated with a low incidence of chronic graft-versus-host disease (GVHD) and high graft-versus-leukemia effects [11, 12]. Here, we hypothesized that these two factors might be associated with favorable long-term outcomes for CBT patients alive in CR 2 years after transplantation. This is clinically relevant since recent breakthroughs in the field of CB expansion might solve the problem of slow engraftment associated with CBT [13, 14]. As control groups, we selected patients given grafts from HLA-matched or HLA-mismatched UD. T-cell replete HLA-

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Table 1. Patient, donor and transplant-related characteristics.

	LEVELS	CBT $N = 364$	UD 10/10 $N = 2648$	Test p value CB vs UD 10/10	UD 9/10 $N = 681$	Test p value CB vs UD 9/10
Age at transplant	Median [IQR]	45.5 [34.1-57.9]	53.6 [42.1-61.3]	<0.0001	50.8 [39.4-59.5]	0.0011
Year of Transplant	Median [IQR]	2011 [2008-2013]	2012 [2009-2014]	<0.0001	2012 [2010-2013]	<0.0001
Patient Sex	Female	192 (52.75%)	1312 (49.57%)	0.255	317 (46.55%)	0.056
	Male	172 (47.25%)	1335 (50.43%)		364 (53.45%)	
	Missing	0	1		0	
Donor Sex	Female	174 (52.25%)	728 (27.87%)	<0.0001	235 (35.66%)	<0.0001
	Male	159 (47.75%)	1884 (72.13%)		424 (64.34%)	
	Missing	31	36		22	
Female to Male donor	No	252 (75.68%)	2335 (89.43%)	< 0.0001	552 (83.76%)	0.002
	Yes	81 (24.32%)	276 (10.57%)		107 (16.24%)	
	Missing	31	37		22	
CMV Patient	Negative	123 (35.86%)	977 (37.61%)	0.53	253 (37.59%)	0.588
	Positive	220 (64.14%)	1621 (62.39%)		420 (62.41%)	
	Missing	21	50		8	
CMV donor	Negative	194 (63.19%)	1524 (58.35%)	0.103	376 (55.79%)	0.029
	Positive	113 (36.81%)	1088 (41.65%)		298 (44.21%)	
	Missing	57	36		7	
CMV donor to patient	Neg to Neg	70 (23.03%)	754 (29.24%)	<0.0001	178 (26.61%)	0.001
	Neg to Pos	122 (40.13%)	748 (29%)		193 (28.85%)	
	Pos to Neg	38 (12.5%)	217 (8.41%)		73 (10.91%)	
	Pos to Pos	74 (24.34%)	860 (33.35%)		225 (33.63%)	
	Missing	60	69		12	
Status of disease at HCT	CR1	229 (62.91%)	2100 (79.31%)	<0.0001	484 (71.07%)	0.007
	CR2	135 (37.09%)	548 (20.69%)		197 (28.93%)	
Secondary AML	No	324 (89.01%)	2223 (83.95%)	0.012	578 (84.88%)	0.064
	Yes	40 (10.99%)	425 (16.05%)		103 (15.12%)	
Cytogenetics	Good	33 (9.07%)	182 (6.87%)	<0.0001	46 (6.75%)	0.014
	Interm	162 (44.51%)	934 (35.27%)		255 (37.44%)	
	Poor	35 (9.62%)	213 (8.04%)		59 (8.66%)	
	NA/failed	134 (36.81%)	1319 (49.81%)		321 (47.14%)	
TBI	No	110 (30.22%)	1943 (73.43%)	<0.0001	521 (76.51%)	<0.0001
	Yes	254 (69.78%)	703 (26.57%)		160 (23.49%)	
	Missing	0	2		0	
MAC conditioning	No	182 (50.42%)	1299 (49.26%)	0.681	313 (46.23%)	0.2
	Yes	179 (49.58%)	1338 (50.74%)		364 (53.77%)	
	Missing	3	11		4	
In vivo TCD	No	247 (71.39%)	682 (25.9%)	<0.0001	111 (16.32%)	<0.0001
	Yes	99 (28.61%)	1951 (74.1%)		569 (83.68%)	
	Missing	18	15		1	
PTCY	No	358 (98.35%)	2589 (97.77%)	0.475	653 (95.89%)	0.032
	Yes	6 (1.65%)	59 (2.23%)		28 (4.11%)	
Karnofsky score	<90	73 (24.66%)	494 (20.05%)	0.063	123 (19.19%)	0.055
	>= 90	223 (75.34%)	1970 (79.95%)		518 (80.81%)	
	Missing	68	184		40	
Previous auto HCT	No	343 (94.23%)	2585 (97.62%)	0.0002	640 (93.98%)	0.87
	Yes	21 (5.77%)	63 (2.38%)		41 (6.02%)	

CBT cord blood transplantation, *UD 10/10* HLA-matched unrelated donor; UD 9/10, 1 out of 10 HLA-mismatched unrelated donor, *HCT* hematopoietic stem cell transplantation, *AML* acute myeloid leukemia, *TBI* total body irradiation, *MAC* myeloablative conditioning regimen, *TCD* T-cell depletion, *PTCY* post-transplant cyclophosphamide.

haploidentical graft recipients could not be added to the comparison since this transplantation approach has only recently emerged in Europe [15].

Here, we thus compared long-term follow-up of patients with AML surviving free of leukemia recurrence for at least 2 years after CBT with that of UD transplantation.

METHODS

Inclusion criteria

This is a retrospective study from the acute leukemia working party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT). The EBMT registry is a voluntary working society of more than 600 transplant centers, participants of which are required once a year to report all consecutive HCTs and follow-up. Audits are routinely performed to check for data accuracy.

Inclusion criteria included: (1) at transplantation: adult patients (defined as ≥18 years of age at transplantation), *de novo* or secondary AML, first or second allo-HCT between 2005 and 2015, CR1 or CR2, either CBT (single or double) or peripheral blood stem cells (PBSC) from HLA-matched UD 10/10 or one locus HLA-mismatched UD 9/10, and no in vitro T-cell depletion of the graft and (2) at the landmark time of 2 years after transplantation: being alive without relapse and without second transplantation.

Statistical analyzes

Analyzes included data from all patients meeting the inclusion/exclusion criteria.

Patient, disease, and transplant-related characteristics for the cohorts (CBT versus UD 10/10 or CBT versus UD 9/10) were compared using the chi-squared test for categorical variables and the Mann-Whitney test for continuous variables.

The primary endpoint was leukemia-free survival (LFS). Secondary endpoints were relapse incidence, NRM, and overall survival (OS). LFS was defined as survival with no evidence of relapse or progression. Relapse was defined as the presence of 5% bone marrow blasts and/or reappearance of the underlying disease. NRM was defined as death without evidence of relapse or progression. OS was defined as the time from transplantation to death, regardless of the cause. Cytogenetic risk group was defined using the MRC classification modified according to Canaani [16]. To accommodate for missing cytogenetic data, 4 cytogenetic risk groups were considered: good, intermediate, poor, and NA/failed. The diagnosis and grading of acute and chronic GVHD were performed by transplant centers using the standard criteria.

Patients were censored at the time of last follow-up. The Kaplan–Meier method was used to estimate the probabilities of OS and LFS. Cumulative incidence functions were used to estimate the endpoints of relapse incidence, NRM, acute and chronic GVHD, to accommodate for competing risks. To study acute and chronic GVHD, we considered relapse and death to be competing events. For death due to GVHD, competing events were death from all other cause.

Univariate analyzes were performed using Gray's test for cumulative incidence functions and the log-rank test for OS and LFS. A Cox proportional hazards model was used for multivariate regression. Variables included in the multivariate Cox model were all those differing significantly in the comparison of patients given a CBT from either a UD 10/10 or a UD 9/10, factors significantly associated with an outcome in univariate analysis, and factors known to be prognostic for AML. Factors included in the model therefore comprised donor type, patient age, patient gender, in vivo T-cell depletion or not, disease status at allo-HCT, primary or secondary AML, cytogenetic risk group, myeloablative versus reduced intensity conditioning, acute GVHD, and chronic GVHD during the first 2 years after allo-HCT. Results were expressed as the hazard ratio (HR) with a 95% confidence interval (95% CI).

All tests were two sided. The type I error rate was fixed at 0.05 for determination of factors associated with time to event outcomes. Statistical analyzes were performed with SPSS 26 (SPSS Inc, Chicago, IL), and R 3.6.1 (R Development Core Team, Vienna, Austria) software packages.

RESULTS

Patients

The number of patients meeting the pre-transplant inclusion criteria but not the landmark inclusion criteria in each group is shown in the Supplementary Table 1. Two-year OS from transplantation for patients meeting the pre-transplant inclusion criteria (irrespective of the status at the 2-year landmark day) were 50.6%, 61.8%, and 54.6% in CBT, MUD and MMUD recipients, respectively (Supplementary Table 2). A total of 3693 patients met the study inclusion criteria at the landmark time. This included 364 CBT recipients, 2648 UD 10/10 patients and 681 patients given grafts from UD 9/10 (Table 1). The median (interquartile age (IQR)) age at transplantation was 46 (18–70) years in CBT recipients, 54 (18–76) years in UD 10/10 recipients ($P < 0.001$) and 51 (18–76) years in those receiving UD 9/10 ($P = 0.001$). The proportion of patients transplanted in CR2 was 37%, 21% ($P < 0.001$) and 29% ($P = 0.007$) in CBT, UD 10/10 and UD 9/10 patients, respectively. Total body irradiation (TBI) was given in 70%, 27% ($P < 0.001$) and 23% ($P < 0.001$) of CBT, UD 10/10 and UD 9/10 recipients, respectively. Extensive chronic GVHD had occurred during the first 2 years after transplantation (before study inclusion) in 10%, 18% ($P < 0.001$) and 17% ($P < 0.001$) of CBT, UD 10/10 and UD 9/10 patients, respectively (Table 2). Finally, in vivo T cell depletion was used less often in CBT (29%) than in UD 10/10 (74%, $P < 0.001$) or in UD 9/10 (84%, $P < 0.001$) patients.

Relapse and non-relapse mortality

The 5-year relapse incidence from transplantation (3 years after the start of the landmark analysis) was 9.8% (95% CI: 6.9–13.3%) in CBT

Table 2. History of GVHD at study inclusion (landmark), 2 years after transplantation.

Variables prior baseline 2 years after HSCT	LEVELS	CBT N = 364	UD 10/10 N = 2648	Test *p* value CB vs UD 10/10	UD 9/10 N = 681	Test *p* value CB vs UD 9/10
Grade II-IV acute GVHD	No	234 (66.67%)	1940 (74.93%)	0.001	488 (74.05%)	0.013
	Yes	117 (33.33%)	649 (25.07%)		171 (25.95%)	
	Missing	13	59		22	
Grade III-IV acute GVHD	No	314 (89.46%)	2446 (94.48%)	0.0002	604 (91.65%)	0.248
	Yes	37 (10.54%)	143 (5.52%)		55 (8.35%)	
	Missing	13	59		22	
Chronic GVHD	No	229 (65.06%)	343 (51.89%)	<0.0001	1397 (53.98%)	0.0002
	Limited	87 (24.72%)	199 (30.11%)		756 (29.21%)	
	Extensive	36 (10.23%)	119 (18%)		435 (16.81%)	
	Missing	12	20		60	

CBT cord blood transplantation, *UD 10/10*, HLA-matched unrelated donor; UD 9/10, 1 out of 10 HLA-mismatched unrelated donor, *GVHD* graft-versus-host disease.

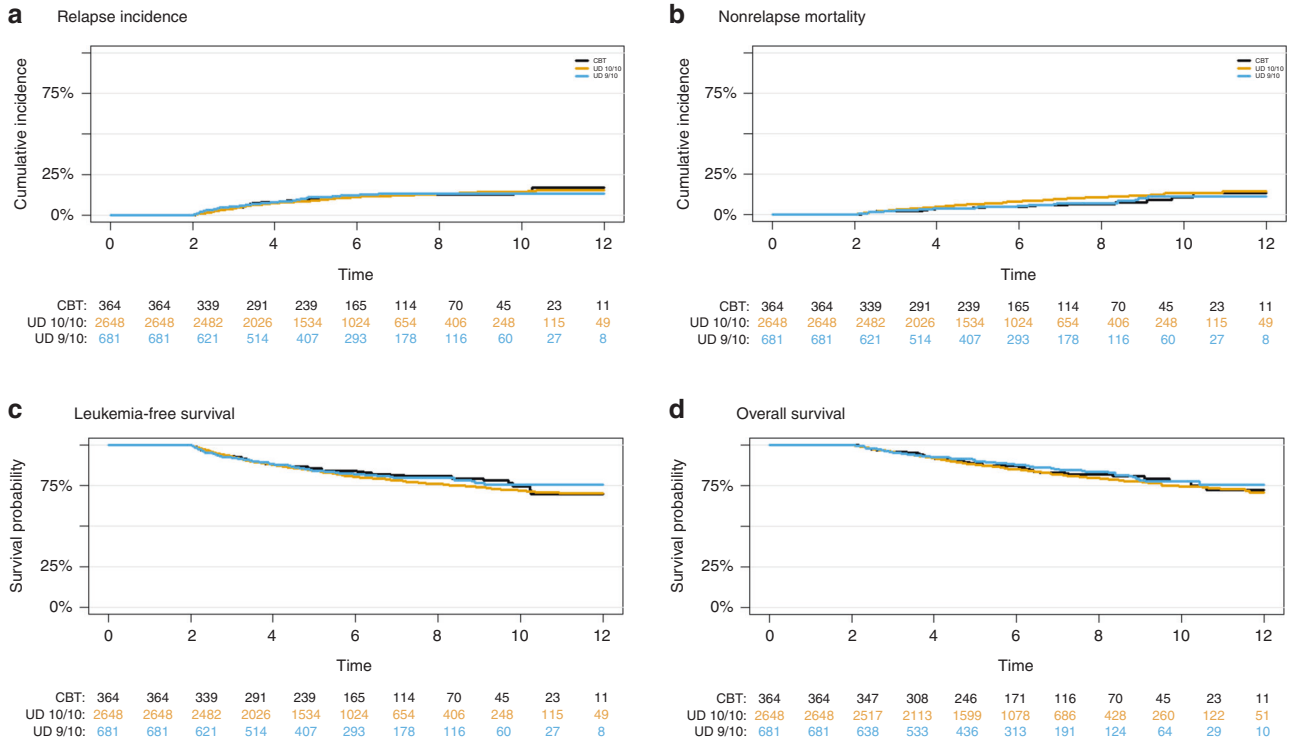

Fig. 1 Long-term transplantation outcomes according to donor type in AML patients alive and in CR, 2 years after transplantation. (**a**) Relapse incidence. (**b**) Nonrelapse mortality. (**c**) Leukemia-free survival. (**d**) Overall survival. *CBT*, cord blood transplantation; UD 10/10, HLA-matched unrelated donor; UD 9/10 1/10 HLA-mismatched unrelated donor.

Table 3. Multivariate analyzes.

		OS		LFS		RI	
Covariates	**Reference**	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
Age at HCT	Five-year increase	1.1 (1.1–1.2)	<0.001	1.1 (1.1–1.1)	<0.001	1.1 (1–1.1)	0.01
Sex patient	Female vs Male	0.8 (0.67–0.96)	0.02	0.74 (0.63–0.87)	<0.001	0.64 (0.51–0.79)	<0.001
In vivo TCD	Yes vs No	0.8 (0.66–0.98)	0.03	0.92 (0.77–1.1)	0.38	1.4 (1.1–1.8)	0.02
Acute GVHD 2–4	Yes vs No	1.1 (0.91–1.4)	0.3	1 (0.84–1.2)	0.99	0.81 (0.63–1)	0.1
Disease status at HCT	CR2 vs CR1	1.2 (0.98–1.5)	0.08	1.2 (1–1.5)	0.05	1.4 (1.1–1.8)	0.01
MAC conditioning	Yes vs No	0.79 (0.64–0.97)	0.02	0.84 (0.7–1)	0.07	1 (0.82–1.3)	0.78
Secondary AML	Yes vs No	1.3 (1–1.6)	0.04	1.3 (1.1–1.6)	0.01	1.4 (1.1–1.9)	0.01
Chronic GVHD before 2 years	Yes vs No	1.8 (1.5–2.1)	<0.001	1.5 (1.3–1.8)	<0.001	1 (0.81–1.2)	0.96
Type of HCT							
UD 10/10	CBT	1.1 (0.81–1.6)	0.47	1.1 (0.83–1.5)	0.42	0.89 (0.6–1.3)	0.57
UD 9/10		1 (0.69–1.5)	0.94	1.1 (0.74–1.5)	0.77	0.9 (0.57–1.4)	0.63
Cytogenetic risks							
Intermediate	Good	1.3 (0.87–2.1)	0.18	1.3 (0.9–1.9)	0.15	1.8 (1.1–3)	0.03
Poor		2 (1.2–3.3)	0.005	1.8 (1.2–2.8)	0.01	2.8 (1.6–5.1)	<0.001
NA/Failed		1.5 (0.98–2.3)	0.06	1.3 (0.93–1.9)	0.12	1.6 (0.96–2.7)	0.07

CBT cord blood transplantation, *UD 10/10* HLA-matched unrelated donor; UD 9/10, 1 out of 10 HLA-mismatched unrelated donor, *HCT* hematopoietic stem cell transplantation, *AML* acute myeloid leukemia, *MAC* myeloablative conditioning regimen, *TCD* T-cell depletion, *OS* overall survival, *LFS* leukemia-free survival, *RI* relapse incidence.

patients, 9.3% (95% CI: 8.2–10.6%) in UD 10/10 patients ($P = 0.85$) and 11.3% (95% CI: 8.9–14.1%) in UD 9/10 patients ($P = 0.93$) (Fig. 1). On multivariate analysis, donor type had no impact on relapse risk (Table 3). Factors associated with a higher relapse incidence included greater age at transplantation (HR by 5-year increase 1.1, 95% CI: 1.0–1.1, $P = 0.01$), in vivo T-cell depletion (HR = 1.4, 95% CI: 1.1–1.8, $P = 0.02$), CR2 versus CR1 (HR = 1.4, 95% CI: 1.1–1.8, $P = 0.01$), secondary AML (HR = 1.4, 95% CI: 1.1–1.9, $P = 0.01$), and poor-risk cytogenetics (HR = 2.8, 95% CI: 1.6–5.1, $P < 0.001$). In contrast, female

Table 4. Cause of death, N (%).

	CBT $N = 55$	UD 10/10 $N = 396$	UD 9/10 $N = 88$
Original disease	23 (44.23%)	124 (37.24%)	32 (39.51%)
Infection	11 (21.15%)	62 (18.62%)	17 (20.99%)
GVHD	1 (1.92%)	70 (21.02%)	17 (20.99%)
Second malignancy	10 (19.23%)	46 (13.81%)	11 (13.58%)
Interstitial pneumonia	3 (5.77%)	4 (1.2%)	0 (0%)
Hemorrhage	1 (1.92%)	3 (0.9%)	0 (0%)
Other transplant-related	3 (5.77%)	24 (6.06%)	4 (4.54%)
Missing	3	63	7

CBT cord blood transplantation, *UD 10/10* HLA-matched unrelated donor; UD 9/10, 1 out of 10 HLA-mismatched unrelated donor, *GVHD* graft-versus-host disease.

recipients had a lower risk of relapse (HR = 0.64, 95% CI: 0.51–0.79, $P < 0.001$).

The 5-year incidence of NRM was 4.5% (95% CI: 2.6–7.1%) in CBT patients, 6.6% (95% CI: 5.6–7.7%) in UD 10/10 patients ($P = 0.12$) and 4.7% (95% CI: 3.2–6.6%) in UD 9/10 patients ($P = 0.91$) (Fig. 1). Since only 15 events occurred in CBT patients, multivariate analysis was not performed for NRM.

Leukemia-free survival and overall survival

The 5-year LFS (primary endpoint) was 85.7% (95% CI: 81.4–89.0%) in CBT patients, 84.0% (95% CI: 82.5–85.5%) in UD 10/10 patients ($P = 0.36$) and 84.0% (95% CI: 80.7–86.7%) in UD 9/10 patients ($P = 0.86$) (Fig. 1). On multivariate analysis, donor type had no impact on LFS. Factors associated with worse LFS included greater age at transplantation (HR by 5-year increase 1.1, 95% CI: 1.1–1.1, $P < 0.001$), CR2 versus CR1 (HR = 1.1, 95% CI: 1.0–1.5, $P = 0.05$), secondary AML (HR = 1.3, 95% CI: 1.1–1.6, $P = 0.01$), antecedent of chronic GVHD (HR = 1.5, 95% CI: 1.3–1.8, $P < 0.001$) and poor-risk cytogenetics (HR = 1.8, 95% CI: 1.2–2.8, $P = 0.01$). In contrast, female recipients had better LFS (HR = 0.74, 95%: CI 0.63–0.87, $P < 0.001$) (Table 3).

The 5-year OS was 88.6% (95% CI: 84.5–91.6) in CBT patients, 87.9% (95% CI: 86.5–89.2%) in UD 10/10 patients ($P = 0.58$) and 89.9% (95% CI: 87.1–92.1%) in UD 9/10 patients ($P = 0.58$) (Fig. 1). In multivariate analysis, donor type had no impact on OS. Factors associated with a worse OS included greater age at transplantation (HR by 5-year increase 1.1, 95% C:I 1.1–1.2, $P < 0.001$), secondary AML (HR = 1.3, 95% CI: 1.0–1.6, $P = 0.04$), antecedent chronic GVHD (HR = 1.8, 95% CI: 1.5–2.1, $P < 0.001$) and poor-risk cytogenetics (HR = 2.0, 95% CI: 1.2–3.3, $P = 0.005$). In contrast, female recipients (HR = 0.80, 95%: CI 0.67–0.96, $P = 0.02$), the use of in vivo T-cell depletion (HR = 0.80, 95%: C:I 0.66–0.98, $P = 0.03$) and myeloablative conditioning (HR = 0.79, 95%: CI 0.64–0.97, $P = 0.02$) were each associated with better OS (Table 3). Interestingly, there was an interaction between donor type and the impact of in vivo T-cell depletion of the graft on OS with the use of in vivo T cell depletion of the graft being associated with better OS in UD recipients but worse OS in CBT recipients (Supplementary Fig. 1).

Causes of death

The main causes of death were original disease in 44%, 37%, and 40% of CBT, UD 10/10, and UD 9/10 recipients, respectively (Table 4). With the exception of fewer deaths from GVHD with CBT, causes of death were comparable across the 3 recipient groups. Cumulative incidence of death related to GVHD at 5 years was 0.28% in CBT versus 2.66% in UD 10/10 and 2.7% in UD 9/10 ($P = 0.004$ and $P = 0.007$, respectively) (Supplementary Fig. 2).

DISCUSSION

Several studies have compared outcomes with CBT versus UD or HLA-haploidentical transplantation. In most of them, median follow-up was relatively short. This might create a bias against CBT which has been associated with delayed engraftment. This might no longer be the case in the near future given impressive results observed with recent techniques of CB expansion [13, 14]. On the other hand, it has been suggested that CBT might be associated with greater graft-versus-leukemia effects than other transplantation approaches [17], perhaps especially in patients with detectable minimal residual disease at transplantation [12, 18]. Furthermore, CBT has been associated with a low incidence of chronic GVHD (which has remained an important cause of mortality >2 years after allo-HCT). Based on these findings, we hypothesized that long-term outcomes might be better for CBT than for UD recipients alive and in CR, 2 years after transplantation. We tested this hypothesis in a large cohort of patients transplanted between 2005 and 2015. Several observations were made.

First, in contrast to our hypothesis, CBT was not significantly associated with a lower late relapse incidence than UD transplantation in the multivariate analysis. This observation contrasts with the hypothesis that CBT is associated with higher graft-versus-leukemia effects than other stem cell sources but supports observations made in a prior study assessing the impact of donor type in patients given grafts after low-dose TBI [8].

A second observation was that there were fewer deaths from GVHD in CBT than in UD recipients. This however did not translate to better OS for CBT because of a small increase in mortality from original disease, infection, and secondary malignancy in CBT patients. The latter (19% versus 14% for CBT versus UD patients, respectively) might be related to the more frequent use of TBI in the conditioning of CBT patients, given prior studies showing that TBI was an important risk factor for second malignancy after transplantation [19]. These observations are in line with a prior report showing that second malignancy was the cause of death in up to 25% of allo-HCT recipients surviving without recurrent malignancy at least 5 years after transplantation [20]. Unfortunately, the design of the study as well as the fact that we do not collect the date of chronic GVHD resolution in the registry precluded us to compare long-term GVHD-free and relapse free survival (GRFS) between the 3 groups. However, a prior study from our group reported that GRFS beyond 100 days was better for CBT than for HLA-identical sibling or MUD recipients in patients given grafts after fludarabine and low-dose TBI regimen [8].

A third observation was that in vivo T-cell depletion of the graft was associated with better long-term OS. This observation is important and demonstrates the need for long-term (beyond 5 years) analyzes of the outcomes of patients included in the phase III studies assessing anti-thymocyte globulin (ATG) for GVHD prophylaxis, since many non-ATG patients were still on systemic immunosuppression (and thus at higher risk of dying) at the latest report of these phase III studies [21–23]. Interestingly, there was an interaction between donor type and the in vivo T-cell depletion of the graft on OS with better OS observed in UD patients given in vivo T-cell depletion but the opposite for CBT recipients. The later observation is in line with prior studies showing that ATG was associated with lower OS in the CBT setting [11, 24].

In addition, this study also underlines that pre-transplant factors associated with early high-risk of relapse such as high-risk cytogenetics, disease status and secondary AML were also predictive of higher risk of late relapse. These data are clinically relevant and might suggest that more frequent monitoring of the original disease is needed in these patients. Interestingly, female gender was associated with a lower risk of relapse as well as better OS and LFS in our study. These results are in concordance with prior observations by our group in a study comparing long-term

outcomes of AML patients older than 50 years and given grafts from HLA-identical sibling or MUD [10].

Myeloablative conditioning was associated with a better survival in this study. This is not surprising given that the impact of regimen-related toxicities is mainly present during the first months after transplantation [25–27], while this landmark analysis include only patients alive in CR, 2 years after transplantation.

There are limitations in the current study including the relative imbalance in the 3 groups, the lack of MRD data, the high proportion of missing cytogenetic data, and the fact that we could not include a T-cell replete HLA-haploidentical cohort of patients since this transplantation approach has only recently emerged in Europe.

In summary, in contrast to our hypothesis, CBT was not associated with a lower frequency of late relapse than UD transplantation. Consequently, long-term LFS/OS for AML patients alive and in CR 2 years after transplantation were not impacted by donor type.

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AUTHOR CONTRIBUTIONS

FB wrote the manuscript, designed the study, and interpreted the data; MN and ML designed the study, analyzed and interpreted the data, and edited the manuscript; AN and MM designed the study, interpreted the data and edited the manuscript; JC, AG, EF, HS, GS, DB, MB, TV, HCR, NK, and AR reviewed and/or edited the manuscript and provided clinical data. All authors approved the final version of the manuscript.

COMPETING INTERESTS

FB has received travel grants and/or speaker honoraria from Celgene, AbbVie, Novartis, Pfizer, and Sanofi. HCR received consulting and lecture fees from Abbvie, AstraZeneca, Vertex and Merck. HCR received research funding from Gilead Pharmaceuticals. HCR is a co-founder of CDL Therapeutics GmbH. The other authors declare that they have no relevant conflict of interest in relation to this study.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The scientific board of the ALWP of the EBMT approved this study. All patients gave informed consent to participate in retrospective studies.

ADDITIONAL INFORMATION

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