ARTICLE

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Comparison of HLA-mismatched unrelated donor transplantation with post-transplant cyclophosphamide versus HLA-haploidentical transplantation in patients with active acute myeloid leukemia

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HLA-haploidentical allogeneic hematopoietic stem cell transplantation (Haplo-HCT) is frequently used as treatment for patients with active acute myeloid leukemia (AML). Here, we investigated whether 9/10 HLA-mismatched unrelated donor transplantation (MMUD-HCT) with post-transplant cyclophosphamide (PTCy) is an adequate alternative. Inclusion criteria in this retrospective registry study consisted of adult patients, first HCT with a Haplo donor or MMUD between 2010 and 2020 using PTCy as graft-versus-host disease (GVHD) prophylaxis, and primary refractory or relapsed disease. MMUD patients were pair-matched 1 to 2 with Haplo-recipients. A total of 73 MMUD patients met the inclusion criteria. Their data were compared to those of 146 Haplo patients in a matched-pair analysis. Median follow-up was 27 months in MMUD patients and 36 months in Haplo recipients. Two-year incidences of relapse and non-relapse mortality (NRM) were 40% and 18% in MMUD patients, respectively, versus 50% ($P = 0.23$) and 24% ($P = 0.18$) in Haplo recipients. Two-year leukemia-free survival (LFS) and overall survival (OS) was 42% and 46% in MMUD recipients, respectively, versus 26% ($P = 0.1$) and 28% ($P = 0.061$) in Haplo-patients. In conclusions, in AML patients with active disease at transplantation, MMUD-HCT results in at least comparable outcomes to Haplo-HCT when PTCy is applied.

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INTRODUCTION

Between 15% and 40% of newly-diagnosed acute myeloid leukemia (AML) patients fail to achieve a complete remission (CR) following intensive induction chemotherapy [1–3]. In addition, AML relapse is by far the leading cause of treatment failure in AML patients not offered an allogeneic hematopoietic stem cell transplantation (allo-HCT) [1–4]. Despite recent progresses in the field, allo-HCT has remained the best treatment option for fit patients with primary refractory or relapsed AML [5, 6]. However, the best donor for this transplantation approach remains to be determined.

Prior studies from our group have assessed the impact of donor type on transplantation outcomes in AML patients with active disease at transplantation [7–9]. One could speculate that

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transplantation approaches with the highest graft-versus- leukemia (GvL) potential should be used in patients with active AML at transplantation. However, although previously associated with high GvL effects [10–13], transplantation outcomes were inferior with umbilical cord blood transplantation (CBT) than with unrelated donor allo-HCT [7]. Other studies have observed similar outcomes with HLA-matched sibling and HLA-matched unrelated donor [8], but lower survival following Haplo-HCT (including both T-cell depleted and T-cell repleted transplants) than with allo-HCT with an HLA-matched sibling donor [9].

While posttransplant cyclophosphamide (PTCy) has revolutionized the field of Haplo-HCT [14–18], recent studies have also demonstrated favorable outcomes with MMUD-HCT when PTCy was used [19–23]. In contrast, PTCy did not seem to improve outcomes following HLA-matched allo-HCT in comparison to antithymocyte globulin (ATG) approaches for AML [18], while it did so in patients transplanted for acute lymphoblastic leukemia [24]. The encouraging results observed with MMUD-PTCy allo-HCT in AML patients, together with the relatively disappointing outcomes observed following Haplo-HCT and CBT in relapsed/refractory AML patients, prompted us to investigate whether MMUD-PTCy allo-HCT would not lead to better outcomes than Haplo-PTCy in patients with active AML at transplantation.

PATIENTS AND METHODS

Study design and inclusion criteria

This study reports the results of a retrospective, multicenter analysis using the dataset of the Acute Leukemia Working Party (ALWP) of the European Society of Bone 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. The results of disease assessments at HCT were also submitted and form the basis of this report.

Inclusion criteria included adult patients (defined as ≥18 years of age at transplantation), first HCT with Haplo donor or MMUD between 2010 and 2020 using PTCy as GVHD prophylaxis, and with primary refractory or relapsed disease.

Ethics

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. EBMT centres commit to obtain informed consent according to the local regulations applicable at the time of transplantation and report pseudonymized data to the EBMT.

Definitions

Reduced intensity conditioning (RIC) was defined as regimens combining fludarabine with either <6 Gy total body irradiation (TBI), ≤ 8 mg/kg busulfan, or ≤140 mg/m^2 melphalan or with other nonmyeloablative drugs as previously reported [10, 11]. Acute and chronic graft-versus-host disease (GVHD) were graded according to previously reported criteria [12]. Comorbidities at transplantation were quantified using the hematopoietic cell transplantation-specific comorbidity-index (HCT-CI) score [25]. Cytogenetic risk was stratified using the MRC-UK classification, as previously reported [26, 27].

Statistical analyses

All MMUD patients meeting the inclusion/exclusion criteria were pair-matched 1 to 2 with Haplo-recipients meeting the inclusion/exclusion criteria ($n = 762$). Matching criteria included status at transplantation (primary refractory versus first relapse versus second relapse, exact pair match), conditioning intensity (RIC versus myeloablative conditioning, exact pair match), Karnofsky performance score (< or ≥90%, exact pair match), and age at transplantation (nearest neighbor).

Start time was the day of allo-HCT for all endpoints. Patients were censored at the time of last follow-up. 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 [28]. Non-relapse mortality (NRM) was defined as death without evidence of relapse or progression. Overall survival (OS) was defined as the time from allo-HCT to death, regardless of the cause. Events in the leukemia-free survival (LFS) included relapse and death, whichever occurred first. Events in 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 [29, 30]. The Kaplan-Meier method was used to estimate LFS, GRFS and OS [31].

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.

Comparison between the 2 groups were performed using cause specific Cox model. In order to take into account correlation between cases and their controls, the multivariate Cox models included a cluster term for each triplet. 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 26.0 (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/).

RESULTS

Patients

A total of 73 MMUD (including 15 8/8 HLA-A, B; C and DRB1 matched unrelated donor) and 762 Haplo-HCT patients met the inclusion criteria. The 73 MMUD patients were matched 1 to 2 with Haplo-HCT patients (patients' characteristics are described in the supplemental Table 1). Accordingly, data from 73 MMUD and 146 Haplo patients were included in the analyses. Median age was 56.1 and 55.6 years in MMUD and Haplo, respectively, ($p = 0.91$). (Table 1). Disease status was primary refractory in 46.6%, first relapse in 43.8% and subsequent relapse in 9.6% of the patients. Cytogenetic risk was intermediate in 45.2% and 52.1%, of the patients, poor in 23.3% and 25.3%, missing for 31.5% and 22.6% of the patients in MMUD and Haplo, repectively ($p = 0.36$). Median year of transplantation was 2017 in both arms ($P = 0.59$). A RIC regimen was used in 59% of the patients, and 63% had a Karnofsky performance score ≥90. Stem cell source was peripheral blood in 89% of MMUD patients versus 68.5% of Haplo-HCT recipients ($P < 0.001$). Post-grafting immunosuppression (in addition to PTCy in all patients) was a combination of a calcineurin inhibitor plus mycophenolate mofetil in 70% of MMUD versus 90% of Haplo-HCT recipients and a combination of sirolimus and mycophenolate mofetil [32, 33] in 7% of MMUD versus 2% of Haplo patients. Median follow-up was 27 (95% confidence interval [CI]: 25–43) months in MMUD versus 36 (95% CI: 26–48) months in Haplo-HCT patients ($P = 0.071$).

GVHD

At 6 months, the cumulative incidences of grade II–IV and III–IV acute GVHD were 35% (95% CI: 24–46%) and 11.3% (95% CI: 5–20%) respectively, in MMUD versus 23% (95% CI: 16–30%, $P = 0.094$) and 8% (95% CI: 4–13%, $P = 0.5$) respectively, in Haplo recipients (Fig. 1 and Table 2). Four cases of grade IV acute GVHD were observed in each group (incidence of 5.6% versus 2.8%). Two-year incidence of chronic GVHD was 26% (95% CI: 15–39%) in MMUD patients versus 21% (95% CI: 15–29%; $P = 0.7$) in Haplo recipients (Fig. 1). For extensive chronic GVHD, the figures were 9% (95% CI: 3–19%) and 7% (95% CI: 4–13%; $P = 0.8$), respectively. Three of the 73 (4%) MMUD patients died of GVHD versus 5 of the 146 (3%) Haplo patients (Table 3).

Table 1. Patient characteristics.

	MMUD ($n = 73$)	Haplo ($n = 146$)	P
Follow-up (mo)			
median (95% CI)	27 [25–43]	36 [26–48]	0.071
Patient age (years)			
median [IQR]	56.1 [46.2–64.1]	55.6 [46.2–63.8]	0.91
Patient sex			
Male	43 (58.9%)	86 (58.9%)	1
Female	30 (41.1%)	60 (41.1%)	
Patient CMV			
Pat. CMV neg.	21 (29.2%)	38 (26.2%)	0.64
Pat. CMV pos	51 (70.8%)	107 (73.8%)	
missing	1	1	
Status at tx			
P refr.	34 (46.6%)	68 (46.6%)	1
Rel1	32 (43.8%)	64 (43.8%)	
Rel2+	7 (9.6%)	14 (9.6%)	
Cytogenetics			
interm	33 (45.2%)	76 (52.1%)	0.36
poor	17 (23.3%)	37 (25.3%)	
NA/failed	23 (31.5%)	33 (22.6%)	
FLT3 [48]			
FLT3-wt	24 (88.9%)	54 (71.1%)	0.072
FLT3-ITD	3 (11.1%)	22 (28.9%)	
missing	46	70	
NPM1			
NPM1 absent	16 (59.3%)	52 (72.2%)	0.22
NPM1 presence	11 (40.7%)	20 (27.8%)	
missing	46	74	
Female -> male			
no F- > M	60 (84.5%)	114 (78.1%)	0.27
F- > M	11 (15.5%)	32 (21.9%)	
missing	2	0	
Stem cell source			
BM	8 (11%)	46 (31.5%)	0.0009
PB	65 (89%)	100 (68.5%)	
Year of tx			
median	2017	2017	0.59
Karnofsky			
<90	27 (37%)	54 (37%)	1
>=90	46 (63%)	92 (63%)	
HCT-CI [25]			
0	21 (43.8%)	50 (47.6%)	
1–2	12 (25.0%)	24 (22.9%)	
>=3	15 (31.3%)	31 (29.5%)	
missing	25	41	
Conditioning			
MAC	30 (41.1%)	60 (41.1%)	1
RIC	43 (58.9%)	86 (58.9%)	
In vivo TCD			
no	59 (80.8%)	124 (84.9%)	0.44
yes	14 (19.2%)	22 (15.1%)	
Associated IS			
CSA	5 (6.8%)	2 (1.4%)	0.0002
MTX	3 (4.1%)	0 (0%)	
MMF	0 (0%)	3 (2.1%)	
TACRO	6 (8.2%)	2 (1.4%)	
CSA + MTX	1 (1.4%)	1 (0.7%)	
CSA + MMF	41 (56.2%)	88 (60.3%)	
MMF + TACRO	10 (13.7%)	44 (30.1%)	
MMF + SIRO	5 (6.8%)	3 (2.1%)	
CSA + MTX + MMF	0 (0%)	1 (0.7%)	
Other	2 (2.7%)	2 (1.4%)	

MMUD 9/10 HLA-matched unrelated donor, *Haplo* HLA-haploidentical transplantation, *mo* months, *CMV* cytomegalovirus, *tx* transplantation, *BM* bone marrow, *PB* peripheral blood, *HCT-CI* hematopoietic cell transplant-specific comorbidity index score, *MAC* myeloablative conditioning, *RIC* reduced-intensity conditioning, *TCD* T-cell depletion, *IS* immunosuppression, *CSA* cyclosporine A, *MTX* methotrexate, *MMF* mycophenolate mofetil, *Tacro* tacrolimus, *Siro* sirolimus.

Relapse and NRM

At 2-years, the cumulative incidence of relapse was 40% (95% CI: 28–52%) in MMUD patients versus 50% (95% CI: 41–59%, $P = 0.5$) in Haplo recipients (hazard ratio [HR] 1.28; 95% CI: 0.86–1.93, $P = 0.23$) (Fig. 2).

At 2-years, the cumulative incidence of NRM was 18% (95% CI: 10–28%) in MMUD patients versus 24% (95% CI: 17–32%, $P = 0.3$) in Haplo recipients (HR 1.50; 95% CI: 0.83–2.71, $P = 0.18$) (Fig. 2).

LFS, GRFS and OS

Two-year probability of LFS was 42% (95% CI: 30–54%) in MMUD patients versus 26% (95% CI: 18–34%) in Haplo recipients (HR 1.35; 95% CI: 0.94–1.93, $P = 0.1$) (Fig. 2). Two-year probability of GRFS was 33% (95% CI: 22–45%) in MMUD patients versus 23% (95% CI: 16–30%) in Haplo recipients (HR 1.19; 95% CI: 0.86–1.64, $P = 0.3$) (Fig. 2). Finally, the 2-year probability of OS was 46% (95% CI: 33–58%) in MMUD patients versus 28% (95% CI: 21–37%) in Haplo recipients (HR 1.42; 95% CI: 0.98–2.04, $P = 0.061$) (Fig. 2).

With respect to cause of death (Table 2), 26 (66.7% of patients who died) MMUD patients versus 68 (65.4%) Haplo recipients died because of their underlying disease and 7 (17.9%) MMUD patients versus 19 (18.3%) Haplo recipients died from an infection.

DISCUSSION

Prior studies have revealed comparable outcomes with HLA-identical sibling or HLA-matched unrelated donors in patients with active AML at transplantation [8]. In contrast, transplantation with CBT and Haplo donors has resulted in lower transplantation outcomes, although comparable outcomes were reported with Haplo-HCT and HLA-identical sibling transplantation in the setting of ATG-based Haplo [34]. Given that encouraging results have been observed with MMUD when PTCy is given for GVHD prophylaxis [22], we performed this retrospective registry study in order to determine whether this approach would result in better outcomes than Haplo-HCT also with PTCy as GVHD prophylaxis in AML patients with active disease at transplantation.

A first observation was that Haplo-PTCy transplantation was used ten times more frequently than MMUD-PTCy in such patients. This could be due to the general thought that Haplo-HCT would be associated with higher GvL effects due to higher genetic disparities. Furthermore, it is likely that many transplant

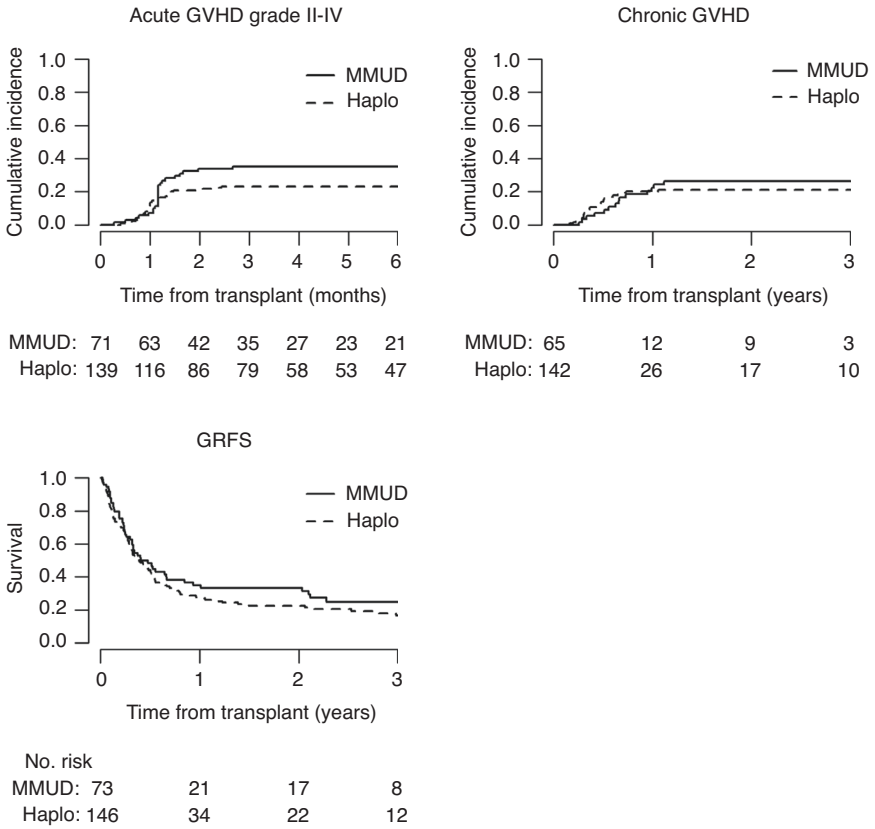

Fig. 1 Cumulative incidence of grade II–IV acute and chronic graft-versus-host disease (GVHD) and severe GVHD and relapse-free survival (GRFS) according to donor type in patients given post-transplantation cyclophosphamide-based GVHD prophylaxis ($P = 0.09$). MMUD, 9/10 HLA-matched unrelated donor. Haplo HLA-haploidentical transplantation.

Table 2. Univariate and multivariate analyses.

Outcome (follow-up)	Univariate analyses			Propensity score matching[a]	
	MMUD	Haplo	*p* value	HR (95% CI)	*p* value (cluster = pairs)
Acute GVHD II–IV (6 months)	35.2% [24.3–46.3]	23% [16.4–30.3]	0.09	0.67 (0.42–1.07)	0.094
Acute GVHD III–IV (6 months)	11.3% [5.2–19.9]	7.9% [4.2–13.2]	0.45	0.73 (0.28–1.93)	0.53
Chronic GVHD (2 years)	26.1% [15.2–38.5]	21.1% [14.5–28.5]	0.64	0.9 (0.49–1.67)	0.74
Extensive chronic GVHD (2 years)	9.2% [3.3–18.7]	7.2% [3.5–12.6]	0.64	0.89 (0.31–2.54)	0.83
Relapse (2 years)	40.2% [28–52.2]	50.2% [41.3–58.5]	0.48	1.28 (0.86–1.93)	0.23
NRM (2 years)	17.6% [9.5–27.6]	24.1% [17.2–31.6]	0.3	1.5 (0.83–2.71)	0.18
LFS (2 years)	42.2% [29.8–54]	25.7% [18.4–33.6]	0.1	1.35 (0.94–1.93)	0.1
OS (2 years)	46.1% [33.1–58.1]	28.4% [20.7–36.5]	0.06	1.42 (0.98–2.04)	0.061
GRFS (2 years)	33.2% [22–44.8]	22.5% [15.7–30.1]	0.31	1.19 (0.86–1.64)	0.3

GVHD graft-versus-host-disease, *NRM* nonrelapse mortality, *LFS* leukemia-free survival, *OS* overall survival, *GRFS* GVHD-free and relapse-free survival.
[a]Matching factors included status at transplantation (primary refractory versus first relapse versus second relapse), conditioning intensity (reduced-intensity versus myeloablative conditioning), Karnofsky performance score (< or ≥90%), and age at transplantation.

centers are waiting for results of ongoing prospective studies of MMUD with PTCy-based GVHD prophylaxis to propose this transplantation option. Because of this imbalance and given the relatively small number of patients included in the MMUD group ($n = 73$), we elected to perform matched-pair analyses between the two donor types.

Despite the higher number of HLA-mismatches in the Haplo group, there was a trend towards a higher incidence of GVHD in the MMUD group. This could be due to the fact that a higher proportion of Haplo patients had GVHD prophylaxis with a combination of a calcineurin inhibitor and mycophenolate mofetil in addition to PTCy. Also, there was a higher proportion of patients given bone marrow stem cells in the Haplo group. Indeed, bone marrow has been associated with a lower incidence of GVHD than peripheral blood stem cells in the Haplo setting [35–39].

Perhaps the most important observation of our study was the suggestion of a better OS with MMUD than with Haplo, although it did not reach statistical significance. These encouraging results suggest that MMUD with PTCy might be an adequate transplant strategy for AML patients with active disease at transplantation who lack an HLA-matched donor.

As expected, relapse was by far the leading cause of treatment failure and of death in both groups. Interestingly, despite higher number of HLA mismatches, relapse incidence was not lower in Haplo than in MMUD patients. This is in line with a prior observations from our group showing similar graft-versus-leukemia effects with HLA-identical sibling donor than with Haplo [40], and could be due to frequent genetic loss of the mismatched HLA-haplotype in patients with active AML at transplantation [41]. In addition, we cannot rule out that the higher use of PBSC in the MMUD group might has contributed to higher GvL effects. Indeed, Bashey et al. observed lower relapse incidence with peripheral blood stem cells than with bone marrow after Haplo transplantation with post-transplant cyclophosphamide in a large registry study [36]. However, we could not confirm these findings in a large cohort of patients with active AML at transplantation [39]. Post-transplant maintenance therapies with FLT3 tyrosine-kinase inhibitors in case of FLT3-ITD AML [42], hypomethylating agents [43, 44] or pre-emptive DLI [45–47] should be investigated in this group of patients.

There are limitations in our manuscript. First, the number of patients in the MMUD group was relatively small ($n = 73$), although we included in the study all MMUD patients meeting the inclusion criteria. In addition, there was a high proportion of missing cytogenetic data (23% and 32% of Haplo and MMUD patients, respectively). Thirdly, out of the 154 centers that contributed patients to this study, only 23 contributed to both MMUD and Haplo patients. Consequently, it was not possible to match for centers in our analyses. Fourthly, given the retrospective nature of our study, we could face unobserved characteristics differing between the 2 groups. However, we ran a pair-match analysis in order to minimize the effects of variables which are unevenly distributed.

In conclusion, our study shows at least comparable outcomes with MMUD-HCT to Haplo-HCT when PTCy-based GVHD prophylaxis is given. These results could serve as the basis for a phase III study comparing these two transplantation approaches.

Table 3. Cause of death[a].

Causes of death	MMUD ($n = 39/73$)	Haplo ($n = 104/146$)
Hemorhage	1 (2.6%)	1 (1%)
Failure/Rejection	0 (0%)	1 (1%)
SOS-VOD	0 (0%)	1 (1%)
Infection	7 (17.9%)	19 (18.3%)
Interstitial pneumonia	0 (0%)	1 (1%)
GVHD	3 (7.7%)	5 (4.8%)
Original disease	26 (66.7%)	68 (65.4%)
Other second malignancy	1 (2.6%)	0 (0%)
Multiple organ failure	0 (0%)	1 (1%)
Other	1 (2.6%)	7 (6.7%)

MMUD 9/10 HLA-matched unrelated donor, *Haplo* HLA-haploidentical transplantation, *SOS-VOD* sinusoidal obstruction syndrome/veno-occlusive disease [49] [50]. *GVHD* graft-versus-host disease.
[a]Percentages are calculated as % of patients who died in this group (39 in MMUD versus 104 Haplo).

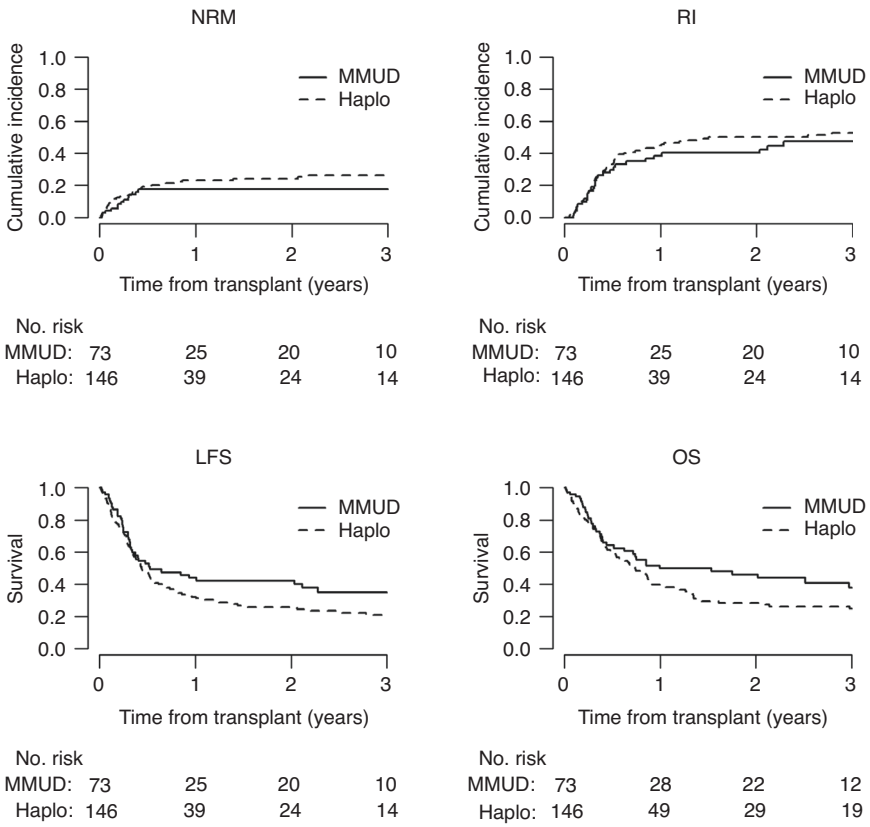

Fig. 2 Transplantation outcomes according to donor type in patients given post-transplantation cyclophosphamide-based GVHD prophylaxis. NRM non-relapse mortality ($P = 0.3$), RI relapse incidence ($P = 0.48$), LFS leukemia-free survival ($P = 0.1$), OS overall survival ($P = 0.06$), MMUD 9/10 HLA-matched unrelated donor, Haplo HLA-haploidentical transplantation.

DATA AVAILABILITY

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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AUTHOR CONTRIBUTIONS

FBa 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. MM and AN designed the study, interpreted the data, and edited the manuscript. JT, FC, AMR, DB, SS, JV, RF, JLDM, CEB, FS, ABu, PJ, YK, PC, EF, WR, JP, AK, AMC, CS, Aba, and PP reviewed the manuscript and provided clinical data. All authors approved the final version of the manuscript.

COMPETING INTERESTS

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