



## Full Length Article

## Allogeneic – Adult

## Haploidentical Versus Matched Unrelated Donor Transplants Using Post-Transplantation Cyclophosphamide for Lymphomas



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## A B S T R A C T

When using post-transplantation cyclophosphamide (PTCy) graft-versus-host disease (GVHD) prophylaxis for lymphoma patients, it is currently unknown whether a matched unrelated donor (MUD) or a haploidentical related donor is preferable if both are available. In this study we wanted to test whether using a haploidentical donor has the same results of a MUD. A total of 2140 adults (34% Center for International Blood and Marrow Transplant Research, 66% European Society for Blood and Marrow Transplantation registry) aged  $\geq 18$  years who received their first haploidentical hematopoietic cell transplantation (haplo-HCT) or MUD-HCT (8/8 match at HLA-loci A, B, C, and DRB1) for lymphoma using PTCy-based GVHD prophylaxis from 2010 to 2019 were retrospectively analyzed. The majority of both MUD and haploidentical HCTs received reduced intensity/nonmyeloablative conditioning (74% and 77%, respectively) and used a peripheral blood stem cell graft (91% and 60%, respectively) and a 3-drug GVHD prophylaxis (PTCy + calcineurin inhibitor + MMF in 54% and 90%, respectively). Haploidentical HCT has less favorable results versus MUD cohort in terms of overall mortality (hazard ratio [HR] = 1.69; 95% confidence interval [CI], 1.30–2.27;  $P < .001$ ), progression-free survival (HR = 1.39; 95% CI, 1.10–1.79;  $P = .008$ ), nonrelapse mortality (HR = 1.93; 95% CI, 1.21–3.07;  $P = .006$ ), platelet engraftment (HR = 0.69; 95% CI, 0.59–0.80;  $P < .001$ ), acute grade 2–4 GVHD incidence (HR = 1.65; 95% CI, 1.28–2.14;  $P < .001$ ), and chronic GVHD (HR = 1.79; 95% CI, 1.30–2.48,  $P < .001$ ). No significant differences were observed in terms of relapse and

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neutrophil engraftment. Adjusting for propensity score yielded similar results. Whenever MUD is available in a timely manner, it should be preferred over a haploidentical donor when using PTCy-based GVHD prophylaxis for patients with lymphoma.

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The use of post-transplantation cyclophosphamide (PTCy) based graft-versus-host disease (GVHD) prophylaxis rapidly expanded because of its promising results in the setting of haploidentical hematopoietic cell transplantation (haplo-HCT) [1]. Initial studies showed acceptable long-term survival and a strikingly low chronic GVHD incidence when using a reduced-intensity conditioning (RIC) and a marrow graft source for both myeloid and lymphoid malignancies [2–4]. Considering the promising and consistent results obtained in the haploidentical setting, retrospective comparisons between haplo-HCT with PTCy and matched-unrelated donor (MUD) HCT with standard GVHD prophylaxis (calcineurin inhibitor [CNI] + mycophenolate [MMF] or methotrexate with or without antithymocyte globulin [ATG]) were made in the setting of both myeloid and lymphoid malignancies [5–8]. Taking into consideration that international guidelines advise use of MUDs as the preferred donor type in the absence of an HLA-matched related donor [7], it is fundamental to understand the real impact of donor type when using PTCy-based GVHD prophylaxis. Although there are ongoing prospective trials to identify the best GVHD prophylaxis in the HLA-matched setting (e.g., PROGRESS 3 trial, NCT03959241), it is difficult to conduct randomized trials based on donor type. Recently, Gooptu et al. [8] performed a comparison between MUD and haploidentical donor transplantation, both using PTCy GVHD prophylaxis, for myeloid diseases. That study demonstrated a substantial survival benefit with MUDs for allogeneic HCT with reduced-intensity conditioning regimen. The aim of our study was to explore the same question in lymphomas.

## MATERIALS AND METHODS

### Data sources

The study was performed through collaboration between the European Society for Blood and Marrow Transplantation (EBMT) and the Center for International Blood and Marrow Transplant Research (CIBMTR) as described elsewhere [9].

### Patients

Included in this analysis are adult ( $\geq 18$  years) patients with Hodgkin (HL) or non-Hodgkin lymphoma (NHL) treated with haplo-HCT or MUD-HCT using PTCy-based GVHD prophylaxis between 2010 and 2019 and reported to either the CIBMTR or EBMT. Recipients of haplo-HCT were mismatched at 2 or more HLA loci, whereas MUD transplants were matched at the allele level at HLA-A, -B, -C, and -DRB1 (8/8). GVHD prophylaxis in both groups included PTCy-based regimens, most commonly in combination with CNI + MMF. Both peripheral blood and bone marrow grafts were included. Myeloablative and non-myeloablative/reduced intensity conditioning were included.

### Definitions

The intensity of conditioning regimens was determined using consensus criteria [10]. Response to last line of therapy before allo-HCT was defined as per Lugano criteria [11].

### Study Endpoints

The primary endpoint overall survival (OS) and secondary endpoints non-relapse mortality (NRM), progression/relapse, progression-free survival (PFS), neutrophil and platelet recovery, acute GVHD and chronic GVHD were calculated using standard criteria [12].

### Statistical analysis

The haplo-HCT cohort was compared against the MUD-HCT cohort. Probabilities of PFS and OS were calculated as described previously [13]. Cumulative incidences of NRM, lymphoma progression/relapse, and hematopoietic recovery were calculated to accommodate for competing risks [14]. The primary analysis

evaluated associations among patient-, disease-, and transplantation-related variables and outcomes of interest using Cox proportional hazards regression. Backward elimination was used to identify covariates associated with outcomes. Covariates with a  $P < .05$  were retained in the models. To adjust for association testing of multiple endpoints, a statistically significant difference was considered when  $P < .01$ . The proportional hazards assumption for Cox regression was tested by adding a time-dependent covariate for each risk factor and each outcome. Covariates violating the proportional hazards assumption were adjusted via stratification in the Cox regression model. Interactions between the main effect and significant covariates were examined. Center effect was adjusted as clusters using the Generalized estimating equation (GEE) approach for all the endpoints [15]. Relative risks were expressed as hazard ratios (HR). Variables considered in the multivariate analyses are shown in Supplementary File 1 of the Supplemental Appendix. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Because of concerns about the potential imbalance of significant risk factors between the haplo-HCT and MUD-HCT cohorts, a sensitivity analysis based on propensity score was also conducted (Supplementary File 2). The propensity score was based on disease, disease stage, donor/recipient cytomegalovirus (CMV) status, HCT-CI, Karnofsky performance status, registry (EBMT versus CIBMTR), patient age, and donor age. Because the maximum unrelated donor age was 55 years old, these additional analyses, including calculation of propensity scores, excluded 260 patients receiving transplants from haploidentical donors older than 55 years old.

## RESULTS

### Baseline Characteristics

The baseline patient-, disease-, and transplantation-related characteristics are shown in Table 1. Lymphoma subtypes in haploidentical transplant recipients were 44% HL and 56% NHL; in MUD recipients they were 28% HL and 72% NHL ( $P < .001$ ). GVHD prophylaxis consisted of PTCy + CNI + MMF in 90% of the haploidentical group and 54% of the MUD group ( $P < .001$ ). The graft source was peripheral blood in 60% ( $n = 1089$ ) of haplo-HCT and 91% ( $n = 283$ ) of MUD transplantations ( $P < .001$ ). The donor age was  $< 40$  in 51% ( $n = 927$ ) of haplo-HCT and 76% ( $n = 236$ ) of MUD ( $P < .001$ ). The maximum MUD age was 55 years.

### OS

The estimated 2-year OS rates were 63% (95% confidence interval [CI], 61–66) and 73% (95% CI, 67–79) in the haplo-HCT and MUD groups, respectively (overall  $P = .007$ ) (Table 2, Figure 1A). In multivariate analysis (Table 3, Figure 2), haplo-HCT was associated with higher overall mortality (inverse of OS) compared to MUD-HCT, (HR = 1.69; 95% CI, 1.30–2.27;  $P < .001$ ). Independent of donor type, pre-HCT disease status being PR or chemoresistant (overall  $P < .001$ ), HCT-CI  $\geq 3$  (HR = 1.47; 95% CI, 1.17–1.86) and Karnofsky performance score  $< 90$  (HR = 1.46; 95% CI, 1.13–1.88;  $P = .004$ ) were associated with poorer survival (Supplementary File 1)

### PFS

The estimated 2-year PFS was 53% (95% CI, 50–55) and 63% (95% CI, 57–69) in the haplo-HCT and MUD groups, respectively (overall  $P = .004$ ) (Table 2, Figure 1B). Multivariate analysis (Table 3, Figure 2) showed that haplo-HCT was associated with higher rates of progression or death (inverse of PFS) compared to MUD-HCT, (HR = 1.39; 95% CI, 1.10–1.79;  $P = .008$ ). Independent of donor type, pre-HCT disease status being PR or chemoresistant (overall  $P < .001$ ), and Karnofsky performance score

**Table 1**Baseline Characteristics of CIBMTR and EBMT Cohorts of Lymphoma Patients Undergoing Haploidentical Related Donor or 8/8 Matched Unrelated Donor Transplantation<sup>a,†</sup>

Variable	Haploidentical	Matched Unrelated	P Value <sup>‡</sup>
Number of recipients	1830	310	
Number of centers	277	103	
Recipient age at transplantation			<0.001
18–29 years	429 (23%)	45 (15%)	
30–39 years	316 (17%)	48 (15%)	
40–49 years	298 (16%)	40 (13%)	
50–59 years	443 (24%)	89 (29%)	
60 years and older	344 (19%)	88 (28%)	
Median (Range)	46 (18–71)	53 (19–71)	<0.001
Sex			0.07
Male	1169 (64%)	214 (69%)	
Female	660 (36%)	95 (31%)	
Missing	1 (<1%)	1 (<1%)	
Karnofsky performance score			0.09
90–100	1282 (70%)	200 (65%)	
10–80	497 (27%)	103 (33%)	
Missing	51 (3%)	7 (2%)	
HCT-CI			<0.001
≤2	1050 (57%)	157 (51)	
>2	362 (20%)	94 (30)	
Missing	418 (23%)	59 (19)	
Lymphoma subtype			<0.001
Follicular Lymphoma	137 (7%)	31 (10)	
DLBCL	447 (24%)	75 (24)	
Mantle cell Lymphoma	178 (10%)	53 (17)	
Classical Hodgkin lymphoma	805 (44%)	86 (28)	
T-cell lymphoma	263 (14%)	65 (21)	
NHL Disease status prior to HCT			0.54
Complete remission	535 (52%)	122 (54)	
Partial remission	317 (31%)	61 (27)	
Chemoresistant	173 (17%)	41 (18)	
HD Disease status before HCT			0.07
Complete remission	397 (49%)	52 (60)	
Partial remission	264 (33%)	18 (21)	
Chemoresistant	144 (18%)	16 (19)	
Prior auto-HCT			0.05
No	736 (40%)	143 (46)	
Yes	1094 (60%)	167 (54)	
Graft type			<0.001
Marrow	741 (40%)	27 (9)	
PBSC	1089 (60%)	283 (91)	
Conditioning regimen intensity			0.23
Myeloablative	415 (23%)	80 (26)	
Non-myeloablative/RIC	1415 (77%)	230 (74)	
GVHD prophylaxis			<0.001
PTCy + CNI + MMF	1647 (90%)	167 (54)	
PTCy + others <sup>c</sup>	183 (10%)	143 (46)	
Time from diagnosis to HCT (mo)			
Median (Range)	29 (3–421)	32 (3–369)	0.88
N Eval	1822	309	
Donor age			<0.001
Less than 20 years	112 (6%)	13 (4)	
20–29 years	392 (21%)	155 (50)	
30–39 years	423 (23%)	68 (22)	
40–49 years	307 (17%)	30 (10)	
50+ years	402 (22%)	7 (2)	

(continued)

Table 1 (Continued)

Variable	Haploidentical	Matched Unrelated	P Value <sup>†</sup>
Missing	194 (11%)	37 (12)	
Median (Range)	37 (12-76)	28 (18-55)	<0.001
Donor/recipient sex match			<0.001
Male-to-male	706 (39%)	166 (54)	
Male-to-female	341 (19%)	55 (18)	
Female-to-male	461 (25%)	44 (14)	
Female-to-female	317 (17%)	39 (13)	
Missing	5 (<1%)	6 (2)	
Donor/recipient CMV match status			<0.001
Donor +/ recipient +	843 (46%)	95 (31)	
Donor +/ recipient –	228 (12%)	36 (12)	
Donor – / recipient +	310 (17%)	77 (25)	
Donor – / recipient –	406 (22%)	94 (30)	
Missing	43 (2%)	8 (3)	
Year of transplant			0.002
2010–2014	529 (29%)	63 (20)	
2015–2019	1301 (71%)	247 (80)	
Follow-up among survivors, Months			
N Eval	1146	231	
Median (25th–75th quartiles)	33 (14–55)	21 (12–35)	<0.001

\* The Pearson chi-square test was used for comparing discrete variables; the Kruskal-Wallis test was used for comparing continuous variables

† Evaluable patients in haploidentical group = 1146 and MUD group = 231.

‡ PTcy + others: CNi only, sirolimus, methotrexate.

<90 (HR = 1.40; 95% CI, 1.17–1.68;  $P < .001$ ) were associated with poorer survival.

### Relapse and NRM

The cumulative incidences of relapse at 2 years were 27% (95% CI, 25–29) and 22% (95% CI, 17–27) in the haploidentical and MUD groups, respectively (overall  $P = .213$ ; Table 2, Figure 1D). Multivariate analysis (Table 3, Figure 2) showed no significant difference in the risk of relapse/progression with haplo-HCT versus MUD (HR = 1.04; 95% CI, 0.78–1.38;  $P = .805$ ). Independent of donor type, HCT done between 2017 to 2019 (compared to 2010–2013 and 2014–2016) was associated with a lower risk for lymphoma relapse, (HR = 0.70; 95% CI, 0.56–0.88;  $P < .001$ ) (Supplementary File 1).

Among recipients of haplo-HCT, the 1-year NRM was 18% (95% CI, 16–20) compared with 12% (95% CI, 8–16) in MUD recipients. The corresponding 2-year NRM was 21% (95% CI, 19–23) and 15% (95% CI, 10–19), respectively (overall  $P = .024$ ; Table 2, Figure 1C). Multivariate analysis showed a significantly higher risk of TRM with haplo-HCT versus MUD HCT (HR = 1.93; 95% CI, 1.21–3.07;  $P = .006$ ). Independent of donor type, older donor age (cutoff for statistical significance  $\geq 50$ ,  $P = .007$ ) and older recipient age  $\geq 50$  (overall  $P < .001$ ) were associated with inferior NRM.

### Hematopoietic Recovery

The cumulative incidence of neutrophil recovery at day 28 was 90% (95% CI, 89–92) in the haploidentical group compared with 93% (95% CI, 90–96) in the MUD group (overall  $P < .001$ ). The day-28 and day-100 cumulative incidences of platelet recovery in similar order were 54% (95% CI, 51–56) and 66% (95% CI, 60–71) and 86% (95% CI, 84–87) and 92% (95% CI, 88–95) (overall  $P < .001$ ; Table 2). Multivariate analysis (Table 3, Figure 2) revealed a slower rate of platelet engraftment in haploidentical compared to MUD transplant

recipients (HR = 0.69; 95% CI, 0.59–0.80;  $P < .001$ ); rates of neutrophil recovery were not statistically different (HR = 0.82; 95% CI, 0.68–0.97,  $P = .025$ ).

Independent of donor type, sex mismatched transplants from female donor to male recipient (HR = 0.86; 95% CI, 0.77–0.95;  $P = .003$ ) and recipient age  $\geq 60$  (overall  $P < .001$ ) were associated with poorer neutrophil recovery (Supplementary File 1). Similarly, platelet recovery was negatively associated with chemoresistant disease status (HR = 0.81; 95% CI, 0.71–0.92;  $P = .001$ ), HCT-CI score  $\geq 2$  (overall  $P \leq .001$ ), time from diagnosis to transplant of 6 to 12 months (HR = 0.61; 95% CI, 0.44–0.84;  $P = .003$ ) and recipient age  $\geq 40$  (overall  $P < .001$ ), whereas donor-positive/patient-negative CMV serological status was associated with better platelet recovery (HR = 1.27; 95% CI, 1.09–1.47;  $P = .002$ ) (Supplementary File 1).

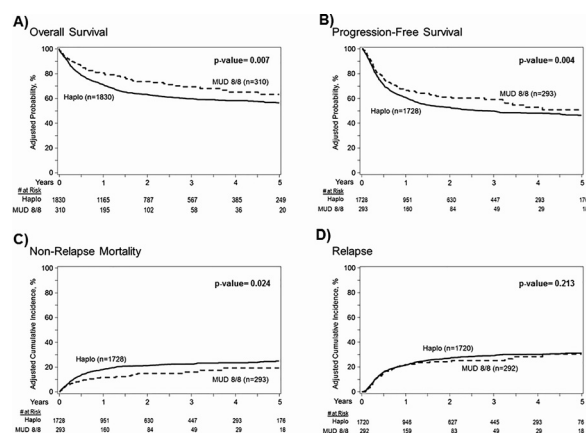
### Acute and Chronic GVHD

Univariate analysis showed the cumulative incidence of grade II–IV acute GVHD at day 100 (Table 2) in the haplo-HCT cohort was 33% (95% CI, 31–35) compared with 24% (95% CI, 20–30) in the MUD group, (overall  $P = .004$ ). The corresponding rates of grade III–IV acute GVHD were 10% (95% CI, 8–11) and 5% (95% CI, 3–8), overall  $P = .018$ . Multivariate analysis (Table 3) showed a higher risk of both grade II–IV acute GVHD (HR = 1.65; 95% CI, 1.28–2.14;  $P < .001$ ) and grade III–IV acute GVHD (HR = 2.04; 95% CI, 1.28–3.25;  $P = .003$ ) in haploidentical compared to MUD transplant recipients.

The cumulative incidences of chronic GVHD at 1 year (Table 2) in the haplo-HCT and MUD groups were 24% (95% CI, 22–26) and 17% (95% CI, 13–22) respectively, overall  $P = .124$ . However, multivariate analysis indicated the risk of chronic GVHD was significantly higher after haploidentical transplantation (HR = 1.79; 95% CI, 1.30–2.48;  $P < .001$ ) relative to MUD allo-HCT (Table 3, Figure 2). In the haplo-HCT group, a

**Table 2**  
Univariate Analysis of Patient Outcomes by Donor Type

Outcomes	Haploidentical		Matched Unrelated		Overall P Value
	N	Prob (95% CI)	N	Prob (95% CI)	
Neutrophil engraftment	1753		292		<.001
28-day		90% (89%-92%)		93% (90%-96%)	
100-day		96% (95%-97%)		98% (96%-99%)	
Platelet recovery	1653		259		<.001
28-day		54% (51%-56%)		66% (60%-71%)	
100-day		86% (84%-87%)		92% (88%-95%)	
Acute GVHD II-IV	1690		279		.004
100-day		33% (31%-35%)		24% (20%-30%)	
Acute GVHD III-IV	1707		286		.018
100-day		10% (8%-11%)		5% (3%-8%)	
Chronic GVHD	1717		277		.124
6 months		14% (12%-16%)		10% (7%-14%)	
1-year		24% (22%-26%)		17% (13%-22%)	
2-year		28% (26%-30%)		23% (18%-29%)	
Relapse	1728		293		.213
100-day		9% (7%-10%)		7% (5%-10%)	
1-year		21% (20%-23%)		20% (15%-25%)	
2-year		27% (25%-29%)		22% (17%-27%)	
Non-relapse mortality	1728		293		.024
100-day		9% (7%-10%)		6% (4%-10%)	
1-year		18% (16%-20%)		12% (8%-16%)	
2-year		21% (19%-23%)		15% (10%-19%)	
Progression-free survival	1728		293		.004
100-day		83% (81%-85%)		86% (82%-90%)	
1-year		61% (58%-63%)		69% (63%-74%)	
2-year		53% (50%-55%)		63% (57%-69%)	
Overall Survival	1830		310		.007
1-year		72% (70%-74%)		80% (75%-85%)	
2-year		63% (61%-66%)		73% (67%-79%)	



**Figure 1.** Kaplan-Meier estimates and cumulative incidence. (A) The 2-year OS was 63% (95% CI, 61%-66%) and 73% (95% CI, 67%-79%) in the haploidentical and matched unrelated groups,  $P = .007$ . (B) The 2-year PFS was 53% (95% CI, 50%-55%) and 63% (95% CI, 57%-69%) in the haploidentical and matched unrelated groups,  $P = .004$ . (C) The 2-year NRM was 21% (95% CI, 19%-23%) and 15% (95% CI, 10%-19%) in the haploidentical and matched unrelated groups,  $P = .024$ . (D) Relapse: 2-year risk of lymphoma relapse was 27% (95% CI, 25%-29%) and 22% (95% CI, 17%-27%) in the haploidentical and matched unrelated groups,  $P = .21$ .

peripheral blood stem cells graft was associated to higher risk of acute grade 2-4 GVHD, acute grade 3-4 GVHD, and chronic GVHD.

### Sensitivity analysis for the primary outcome of overall mortality: Inverse Probability Treatment Weighting Regression Using Propensity Score (PS) Weighting and Propensity Score Matching Analysis

Considering the heterogeneity of the study population, particularly with regard to patient and donor age, 2 sensitivity analyses using propensity scores on a restricted subcohort of patients receiving transplants from donors age  $\leq 55$  years old were conducted. The PS was based on disease, disease stage, donor CMV status, HCT-CI, Karnofsky performance status, registry, patient age, and donor age (Supplementary File 2). Both sensitivity analyses confirmed multivariate results, whether patient age and donor age were considered as continuous or categorical variables in the PS modeling. Considering ages as continuous variables, the Inverse Probability Treatment Weighting weighted Cox model for overall mortality (1 -OS) with haploidentical versus MUD HCT show a HR of 1.38 (95% CI, 1.03-1.85;  $P = .03$ ). Considering age as categorical variables, the HR was 1.36 (95% CI, 1.01-1.83;  $P = .04$ ).

**Table 3**

Multivariate Analysis of Transplant Outcomes by Donor Type

Outcome by Donor Type	Evaluable	Events	HR (95% CI)	P Value
Neutrophil engraftment <sup>*</sup>				
Haploidentical	1753	1681	0.82 (0.68–0.97)	.025
Matched unrelated	292	288	1.00	
Platelet recovery <sup>†</sup>				
Haploidentical	1645	1423	0.69 (0.59–0.80)	<.001
Matched unrelated	258	243	1.00	
Acute GVHD II–IV <sup>‡</sup>				
Haploidentical	1690	590	1.65 (1.28–2.14)	<.001
Matched unrelated	279	71	1.00	
Acute GVHD III–IV <sup>§</sup>				
Haploidentical	1707	179	2.04 (1.28 – 3.25)	.003
Matched unrelated	286	17	1.00	
cGVHD <sup>  </sup>				
Haploidentical	1721	464	1.79 (1.30–2.48)	<.001
Matched unrelated	277	58	1.00	
Relapse <sup>*</sup>				
Haploidentical	1720	465	1.04 (0.78–1.38)	.805
Matched unrelated	292	63	1.00	
Non-relapse mortality <sup>#</sup>				
Haploidentical	1728	367	1.93 (1.21–3.07)	.006
Matched unrelated	293	41	1.00	
Progression or death <sup>**</sup>				
Haploidentical	1728	838	1.39 (1.10–1.79)	.008
Matched unrelated	294	104	1.00	
Overall mortality <sup>††</sup>				
Haploidentical	1830	684	1.69 (1.30–2.27)	<.001
Matched unrelated	310	79	1.00	

\* Adjusted by patient age, HCT CI, sex match; stratified by population resources, GVHD prophylaxis, graft type and conditioning regimen.

† Adjusted by patient age, HCT CI, CMV match, disease stage, time from diagnosis to transplant; stratified by population resources, GVHD prophylaxis, graft type and conditioning regimen.

‡ Adjusted by donor age, HCT CI; stratified by population resources, GVHD prophylaxis, graft type and conditioning regimen.

§ Adjusted by previous auto HCT; stratified by population resources, GVHD prophylaxis, graft type and conditioning regimen.

|| Adjusted by previous auto HCT; stratified by population resources, GVHD prophylaxis, graft type and conditioning regimen.

\* Adjusted by year of transplant; stratified by disease stage, time from diagnosis to transplant, population resources, GVHD prophylaxis, graft type and conditioning regimen.

# Adjusted by patient age, disease stage, donor age, CMV match, Karnofsky score; stratified by population resources, GVHD prophylaxis, graft type and conditioning regimen.

\*\* Inverse of progression-free survival; adjusted by disease stage, CMV match; stratified by disease type, donor age, population resources, GVHD prophylaxis, graft type and conditioning regimen.

†† Inverse of overall survival; adjusted by patient age, disease stage, HCT CI, CMV match, Karnofsky score; stratified by disease type, donor age, population resources, GVHD prophylaxis, graft type and conditioning regimen.

A propensity score matched-pair analysis was also performed. We were able to match 273 pairs. Treating age as a continuous variable, there was no difference in propensity scores ( $P = .96$ ), patient age ( $P = .48$ ), or donor age ( $P = .26$ ) between haplo-HCT and MUD HCT recipients in the matched cohort. The HR for overall mortality with haploidentical versus MUD was 1.49 (95% CI, 1.09–2.04),  $P = .012$ . Considering age as a categorical variable, there was again no difference in propensity scores or donor or patient age between haploidentical and HCT recipients in the matched cohort, and the HR for mortality was 1.58 (95% CI, 1.16–2.16;  $P < .01$ )

### Causes of Death

With a median follow-up of 33 months (range 0–123) in the haplo-HCT and 21 months (range 0–108) in the MUD group, numbers of deaths in both groups at last follow-up were 684 and 79, respectively. As reported by the treating institution, lymphoma relapse/progression was the cause of death in 244 (36%) and 29 (37%) of patients in the haplo-HCT and MUD

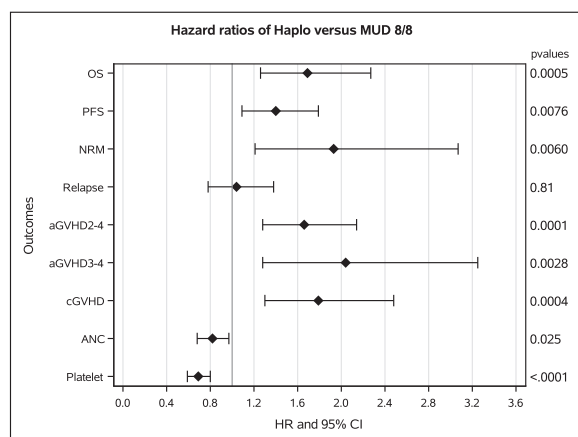
recipients, respectively, making it the most common cause of death in either group (Table 4). Other leading causes of deaths were infection followed by GVHD in both haplo-HCT and MUD recipients. It should be noted that cause of death data was missing in 23 (3%) of haplo-HCT and 5 (6%) of MUD patients.

### DISCUSSION

The advent and widespread use of PTCy-based GVHD prophylaxis to successfully perform HLA-mismatched transplantation has made haploidentical donors an acceptable graft source that is rapidly available for the vast majority of patients, even those under-represented in international donor registries [16]. Nevertheless, the existing evidence did not allow us to know whether this is the best approach if using PTCy-based GVHD prophylaxis for MUD HCT.

In the current study, where all transplantations were done using the PTCy platform, the use of MUDs was associated with a significant advantage in OS. This effect was explained by lower NRM and GVHD incidences. No significant differences





**Figure 2.** Forest plot showing the results of multivariate analysis of patients with lymphomas undergoing haploidentical donor versus matched unrelated donor allogeneic transplantation using post-transplantation cyclophosphamide-based GVHD prophylaxis. HR to the right of 1.0 favor MUD for all outcomes except ANC and platelets. For ANC and platelets, HR to the left of 1.0 favor MUD.

were observed in relapse. These results are in line with a recent study from Gooptu et al. [8], where a survival advantage of MUDs over haploidentical donors in the myeloid RIC setting was explained by a higher NRM, driven in part by more frequent acute GVHD. In our study, almost 70% of patients in both cohorts received RIC, which is expected in a lymphoma cohort. Compared to the Gooptu study, we also observed an association between a higher chronic GVHD incidence and the use of a haploidentical donor. A second difference between the 2 groups was the shorter platelet engraftment time of the MUD cohort. This could be explained by the more prevalent use of peripheral blood stem cell graft in this group. This difference has been previously documented both in the use of standard CNI-based GVHD prophylaxis and HLA-matched donors [17] and in the haploidentical setting with PTCy [18]. However, other studies reported in literature are describing different results when comparing haplo-HCT to MUD in lymphomas. In a recent metaanalysis by Gagelmann et al. [19], showed that haplo-HCT with PTCy had increased relapse than MUD for lymphoma patients. However, in that large metaanalysis, GVHD prophylaxis for the MUD cohort was ATG-based in most cases.

This analysis also shows that PTCy can be used for MUD HCT. We previously demonstrated 3-year OS rates of 62% and 50% for MUDs with standard calcineurin inhibitor GVHD prophylaxis, without or with ATG, respectively [6]. The 72% 2-year OS after MUD HCT cohort in the current study, using PTCy, compares well with these previously published results. The same is true for relapse incidence (28% and 36% at 3 years versus 22% at 2 years), NRM (13% and 20% versus 12% at 1 year), PFS (49% and 28% at 3 years versus 63% at 2 years), grade 2-4

acute GVHD (40% and 49% versus 24% at day +100) and chronic GVHD (51% and 33% versus 17% at 1 year). Prospective trials, including the CTN PROGRESS 3 study (NCT03959241), are addressing this question in a randomized fashion. Although the use of PTCy should not yet be considered standard, a recent prospective phase 2 study from Shaw et al. shows how such a platform could be safely used for HLA mismatched unrelated donor HCT (with bone marrow graft) [20], making it an attractive platform to expand the donor pool to races and ethnicities underrepresented in donor registries. However, other differences such as infections incidence (e.g., viral reactivations, fungal infections) should also be considered while comparing different GVHD prophylaxis [21]. In our study, causes of death related to infectious complications were similar between the two types of donor. This was in line with previous reports [22].

A third significant observation in our study is related to the HL subset analysis. No significant differences between haploidentical or MUD donors were confirmed in the HL population (Supplementary File 3). Probably, the low number of patients and short follow-up of the MUD cohort did not allow the study to have sufficient statistical power.

This study has some limitations. The inclusion of PTCy as GVHD prophylaxis platform in the MUD setting is quite recent. The number of reported patients is limited, and this fact might compromise the statistical power to detect small differences in outcomes. To overcome this issue, a joint study between CIBMTR and EBMT, the 2 largest HCT registries in the world, was made. Second, we do not know how centers performed donor selection. It is possible that a few centers preferred haploidentical donor over MUD donor based on institutional preference or because of time restrictions whereas others deferred use of a haploidentical donor until a MUD search was unsuccessful, which could introduce bias. However, we believe that a prospective randomized study between MUD and haploidentical donors would be extremely difficult to conduct because both types of donors may not be available for all patients. Another issue is the heterogeneity of the study population in terms of donor registry, GVHD prophylaxis, graft source, conditioning regimen and donor age. All these factors were included and adjusted for in the multivariate analyses. Results were also confirmed independently in two sensitivity analyses that incorporated propensity scores to further adjust for population differences. Regarding the use of different GVHD prophylaxis, we can observe that the MUD cohort received more heterogeneous prophylaxis regimens instead of the classic PTCy + CNI + MMF. Specifically, in the MUD cohort there was a higher percentage of patients who received a 2-drug (PTCy + CNI) instead of classic 3-drug GVHD prophylaxis (0.7% versus <0.1%). We know from a previous study from the EBMT that a 3-drug PTCy-based GVHD prophylaxis has a better GVHD and relapse-free survival [23]. Despite this, the MUD cohort had a lower GVHD incidence, possibly suggesting that a 2-drug PTCy-based GVHD prophylaxis can be sufficient in this setting. This has been reported in a recent study by Mehta and colleagues [24]. Of note, in a recent prospective randomized study made in HLA-identical donors, the sole use of PTCy without additional drugs had same results that standard CNI-based GVHD prophylaxis [25]. Another critique could be related to the higher use of BM graft in the haploidentical cohort. To compensate for different use of graft sources, we performed an analysis restricted to peripheral blood stem cell population (Supplementary File 4) confirming general results. Also, the study population is quite heterogeneous in terms of disease type between the two groups. This could limit the analysis of the graft-versus-lymphoma effect, which is different depending on lymphoma subtype. Finally, median donor

**Table 4**  
Causes of Death

Cause of Death	Haploidentical*	Matched Unrelated†
Primary Disease	244 (36%)	29 (37%)
GVHD	95 (14%)	9 (11%)
Infection	197 (29%)	22 (28%)
Other Causes	125 (18%)	14 (18%)
Missing	23 (3%)	5 (6%)

\* No. of deaths = 684.

† No. of deaths = 79.

age was higher in the haploidentical group (37 years versus 29 years). Adjustments for age were performed in 2 separate analyses. In addition, in a recent retrospective study from Perales et al. [26] comparing MUD with standard GVHD prophylaxis versus haplo-HCT with PTCy for acute myeloid leukemia, donor age had no significant impact on survival. The same results were confirmed on a large retrospective analysis on haplo-HCT with PTCy where donor age did adversely affect survival despite being associated with higher acute GVHD and NRM incidence. The latter was counterbalanced by less relapse [27]. Prospective data could help to further address this question.

In conclusion, our results suggest that use of a MUD over a haploidentical donor when using PTCy-based GVHD prophylaxis could be preferable for non-Hodgkin lymphoma patients. The data do not support favoring a haploidentical donor if a MUD is available in a timely manner. MUD donors are unfortunately less of an option for the majority of patients/recipients of non-European Caucasian descent who either do not have quick access to an 8/8 MUD donor or have no 8/8 MUD donor prospect. For this large group, haploidentical transplantations result in acceptable outcomes for this high-risk disease population. Moreover, PTCy seems to be a valid alternative to standard CNi-based GVHD prophylaxis for MUD HCT. Clinical differences between the MUD and haploidentical cohorts such as a different use of graft sources (bone marrow was mostly used in the haploidentical cohort) or type of registry (CIBMTR versus EBMT) could have biased these results, and prospective trials are awaited in this setting.

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#### SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jct.2022.11.028.

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