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Matched unrelated donor transplantation *versus* haploidentical transplantation with post-transplant cyclophosphamide in children with acute myeloid leukemia: a PDWP-EBMT study

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ABSTRACT

In children with acute myeloid leukemia (AML) who lack an HLA identical sibling, the donor can be replaced with an HLA matched unrelated donor (MUD) or a haploidentical donor (haplo). We compared outcomes of patients <18 years with AML in first and second complete remission (CR1 & CR2) undergoing a hematopoietic stem cell transplantation (HCT) either with a MUD with anti-thymocyte globuline (ATG) (n=420) or a haplo HCT with PT-CY (n=96) after a myeloablative conditioning regimen (MAC) between 2011 and 2021, reported to EBMT. A matched pair analysis was performed to adjust for differences among groups. The final analysis was performed on 253 MUD and 95 haplo-HCTs. In the matched cohort, median age at HCT was 11.2 and 10 years and median year of HCT was 2017 and 2018, in MUD and haplo-HCT recipients, respectively. The risk of grade III-IV aGvHD was significantly higher in the haplo group (HR=2.33, 95%CI1.18-4.58, p=0.03). No significant differences were found in 2 years overall survival (OS; 78.4%vs71.5%; HR 1.39, 0.84-2.31, p=0.19), leukemia-free-survival (LFS; 72.7%vs69.5%; HR1.22, 0.76-1.95, p=0.41), CI of relapse (RI; 19.3%vs19.5%; HR=1.14, 0.62-2.08, p=0.68) non-relapse-mortality (NRM; 8%vs11%; HR=1.39, 0.66-2.93, p=0.39) and graft versus host free-relapse free survival (GRFS; 60.7%vs54.5%, HR=1.38, 0.95-2.02, p=0.09) after MUD and haplo-HCT respectively. Our study suggests that haplo-HCT with PT-CY is a suitable option to transplant children with AML lacking a matched related donor.

INTRODUCTION

Childhood acute myeloid leukemia (AML) is a rare and heterogeneous disease, with an incidence of 7 cases per million children younger than 15 years. [1] Improvements in genomic characterization, disease response monitoring, [2] as well as the introduction of new drugs [3] and advances in allogeneic hematopoietic cell transplantation (HCT) techniques [4] have resulted in improved outcomes with survival rates reaching 70% in high-income countries. First line treatment approaches for pediatric AML include four or five cycles of myelosuppressive chemotherapy followed by HCT for high-risk patients [5], while HCT is offered in second clinical remission for other cases. [5,6]

In recent years, the development of HCT from alternative donors, preferably from matched unrelated donors (MUD), has provided the means to offer HCT, when no HLA matched family donor is available. But in up to 40% of patients a MUD cannot be identified in international donor registries. [7] Recently, HCT

from relatives sharing only one HLA-haplotype with the recipient (haplo-HCT) has emerged as a suitable alternative, with the great advantage that haplo-donors may be available for almost all patients, in due time, with a flexible schedule and additional cellular therapies being readily available.

In haplo-HCT, different techniques to overcome the HLA barrier[8–12] have been developed for improving immune reconstitution and graft-versus-leukemia with no excess of graft versus host disease (GVHD). In the last years, the use of T-cell replete haplo-HCT with post-transplant cyclophosphamide (PT-CY), [8] has rapidly increased across the world, showing identical clinical outcomes to matched donors (MDs) in several retrospective studies in adults. [8]

Many studies demonstrated that PT-CY given after graft infusion can eliminate alloreactive T cells while preserving hematopoietic cells as well as memory and regulatory T cells.[13,14] In pediatric patients affected by acute leukemia, promising clinical results have been reported, [13,15–19] but specific data on AML are lacking.

Here, we compared the results of a haplo-HCT with PT-CY to a MUD HCT using anti-thymocyte globulin (ATG) for the treatment of children affected by AML reported to the European Society for Blood and Marrow Transplantation (EBMT) registry.

METHODS

Study design and definitions

This multicenter retrospective study was conducted on behalf of the Pediatric Diseases Working Party (PDWP) of EBMT after approval by the institutional review board of the PDWP. Data were collected according to EBMT rules. Patients or legal guardians provided written informed consent for data collection and analysis in accordance with the Declaration of Helsinki. Included were pediatric patients (age <18 years) diagnosed with AML, transplanted in first or second complete remission from 2011 to 2021, who underwent a first allo-HCT using either a 10/10 MUD with ATG or a haploidentical family donor (≥2 recipient-donor HLA mismatch number) in a haplo-HCT with PT-CY. Transplants were performed in 117 EBMT centers. All patients received a myeloablative conditioning (MAC) regimen, and the graft source was bone marrow or peripheral blood, according to the transplant center policy. In patients receiving ex-vivo T-cell depletion, Alemtuzumab or a combination of ATG and PT-CY was excluded.

Outcomes

The primary objective was to compare the leukemia-free survival (LFS) of AML patients receiving either a haplo-PT-CY or a MUD-ATG HCT. The secondary objectives were the comparison of overall survival (OS), non-relapse mortality (NRM), relapse incidence (RI), incidence of both acute (aGvHD) and chronic GvHD (cGvHD), GvHD-free/relapse-free survival (GRFS) in both groups. LFS was defined as time from HCT to first event of relapse or death. OS was defined as the time from HCT to death from any cause. RI was defined as the time from HCT to the first event of leukemia recurrence. Non-relapse mortality (NRM) was defined as death without evidence of relapse. RI and NRM were mutually competing events. GRFS was defined as the time from HCT to the first event among grade III-IV acute GVHD, extensive cGVHD, relapse, and death. [20] Grade II-IV aGVHD and cGVHD were assigned and graded using standard criteria. [21, 22] Competing events of aGVHD and cGVHD were relapse and death. Cytogenetics abnormalities were classified according to the genetically defined prognostic stratification of the the 2017 European Leukemia Net cytogenetic classification system.[1] Neutrophil recovery was defined as the time from HCT to the first of three consecutive days with neutrophil counts above 0.5 x 10^9/l; Platelet recovery was defined as independence from platelet transfusion for at least 7 days with a platelet count of more than >20 × 10^9/L. Death and consecutive HCT were competing events.

Statistical analysis

The overall population included 420 MUD and 96 haplo PTCY. A matched pair analysis was performed to reduce or eliminate confounding factors: The matching included exact match on disease status, cell source and age group at HCT, and nearest match on year of HCT, age at diagnosis, female donor to male recipient, Lansky score and CMV match. A maximum of three MUD matched patients was allowed for one Haplo PT-CY. There were 3 controls for 73, 2 for 12 and 1 for 10 haplo PT-CY. For one haplo PT-CY it was not possible to find a control. Finally, a match could be identified for 253 MUD and 95 haplo PT-CY.

Median values with respective interquartile ranges (IQR), were used to express quantitative variables while frequencies and percentages were used for categorical variables. On the unmatched population, differences between MUD and haplo PT-CY on quantitative and qualitative variables have been tested using Chi-square and Wilcoxon tests respectively. LFS, OS and GRFS have been estimated using the Kaplan-Meier estimator. All outcomes with competing events have been estimated using the cumulative incidence function. Median follow-up was estimated using the reverse of the Kaplan-Meier method. All outcomes have been censored at last follow-up or at 2 years due to a different follow-up between the

groups. Differences in outcomes have been tested using a Cox model including a cluster term for each pair. Results have been expressed as Hazard Ratio (HR). Outcomes and HR have been presented with their 95% confidence interval. All tests were two-sided with an error rate fixed at 5%. Analyses have been done using R statistical software version 4.0.2 (http://www.R-project.org), and matching was performed using the MatchIt package.

RESULTS

Patients and transplant characteristics

Patient and transplant characteristics are summarized in Table 1. Overall, 96 and 420 patients receiving a haplo PT-CY or MUD HCT, respectively, fulfilled the inclusion criteria. Median age at transplant was 9.8 (IQR 3.0 -15.2) years for haplo PT-CY and 7.7 (IQR 2.8-13.6) years for MUD (p=0.03).

Patients in the haplo group were transplanted more recently (median 2018 for haplo vs 2016 for MUD, p<0.01). In both groups the majority of patients were in CR1 at transplant (72.9% haplo vs 70.5% MUD, p= 0.63).

Cytogenetic risk at diagnosis was not significantly different in the two groups (good: 21.3% vs 13.6%, intermediate: 48% vs 44.3%, poor: 30.7% vs 42.1% in haplo PT-CY and MUD respectively).

Donors were older in the haplo PT-CY than in the MUD cohort: 35.7 years (IQR: 29.9-42.7) vs 27.7 years (IQR 23.3-34.2, p<0.01). Bone marrow (BM) was the most frequently used stem cell source in both groups (65.6% for haplo vs 63.6% for MUD; p=0.71).

Conditioning regimen was MAC, mainly based on busulfan (Bu), with Bu/Fludarabine (66.7%) based in the haplo PT-CY and Bu/CY (28.8%) or Bu/CY/melphalan (38.3%) being the most common in MUD.

Post-HCT immunosuppression consisted mainly of cyclosporine (CSA) plus mycophenolate mofetil (MMF) in the haplo PT-CY (52.1%) and CSA plus methotrexate (MTX) in the MUD cohort (68.6%).

The baseline characteristics of the matched cohort were described in Table 2.

Engraftment, acute and chronic GVHD

The CI of day 60 neutrophils and day 180 platelet recovery for haplo PT-CY was 90.4% (95%CI 82-95) and 92.2% (95%CI 82.6-96.6) while for MUD was 97.1% (95%CI 93.9-98.6) and 93.8% (95%CI 89.1-96.4) respectively.

100d grade II-IV aGVHD was 36.7% (95%CI 26.8-46.6) for haplo PT-CY and 28.7% (95% CI 23.2-34.4) for MUD and CI of grade III-IV acute aGvHD was 14.4% (95%CI 8.1-22.5) vs 6.4% (95%CI 3.8-9.9), respectively.

2y CI of cGVHD was 22.4% (95%CI 13.4-32.8) and 18.5% (95%CI 13.5-24.1) for Haplo PT-CY and MUD respectively; 2y CI of extensive cGVHD was 6.6% (95% CI 2.4-13.8) and 8.6% (95% CI 5.3-13) for haplo PT-CY and MUD (Table 3).

According to donor type, there were no statistically significant differences between groups on the incidence of grade II-IV aGvHD (HR=1.26, 95%CI0.84-1.89, p=0.27), cGVHD (HR=1.81, 0.75-4.37, p=0.19) and extensive cGVHD (HR=1.01, 95%CI0.25-4.03, p=0.99). The risk of grade III-IV aGvHD was significantly higher in haplo PT-CY (HR=2.33, 95% CI 1.18-4.58, p=0.03) (Table 4).

Main outcomes

Results of the punctual estimation of outcomes after matched-pair analysis are summarized in Table 3.
The 2-yr CI of RI was 19.5% (95% 11.4-29.2) for haplo PT-CY vs 19.3% (95%CI 14.4-29.4) for MUD. The 2-yr NRM was 11% (95%CI 5.2-19.1) vs 8% (95%CI 5-11.9) after haplo PT-CY and MUD respectively.

The 2-yr OS was 71.5% (95%CI 59.1-80.7) and 78.4% (95%CI 72.2-83.4), the 2-yr LFS was 69.5% (95%CI 57.7-78.6) and 72.7% (95%CI 66.3-78.1) and the 2-yr GRFS was 54.5% (95%CI 42.5-65) and 60.7% (95%CI 53.8-66.9) for haplo PT-CY and MUD respectively (Figure 1).

The most common causes of death were disease recurrence (61.9% in the haplo and 59.6% in the MUD group, respectively), infections (28.6% vs 19.1%), and GVHD (9.5% vs 8.5%).
There were no statistically significant differences between groups on RI (HR=1.14 95%CI 0.62-2.08, p=0.68), NRM (HR=1.39, 95%CI 0.66-2.93), p=0.39), OS (HR 1.39, 95%CI 0.84-2.31, p=0.19), LFS (HR 1.22, 95%CI 0.76-1.95, p=0.41) and GRFS (HR 1.38, 95%CI 0.95-2.02, p=0.09) (table 4).

DISCUSSION

Allogeneic HCT from MUD remains the standard of care in patients who lack a MSD, especially for pediatric patients in which transplant related toxicities and late effects are particularly relevant with regard to a long life expectancy. [23–28] The recent emergence of HLA haplo-HCT extended the availability of donors to most pediatric patients without a MD.[29] Significant improvements of supportive care and the

technical development of highly effective T depleted and T cell replete HLA –haploidentical platforms, have resulted in improved outcomes and reduced transplant related mortality for patients undergoing haplo-HCT, [30] independently of the haplo platform used. [31,36,37]

T cell depleted haploidentical platforms have been successfully used despite high costs for graft processing and specialized expertise. [11,32,33] Of particular interest, Locatelli et al [10] reported the outcome of a cohort of 80 children with acute leukemia transplanted from a haplo donor after αβ T cell and CD19+ B cell depletion. All children received a myeloablative conditioning and ATG for GVHD prophylaxis and graft rejection; no post-transplant GVHD prophylaxis was given. The 5-yr OS was 72% and LFS 71% with no differences in AML and ALL. TRM was 5% and RI was 24%. No patients developed grade II-IV aGVHD with visceral involvement, grade III-IV aGVHD or cGVHD. Bertaina et al. [12] compared the outcomes of 98 children treated with αβ T cell depletion compared with 127 MUD and 118 mismatched UD (MMUD). 5-yr LFS was not significantly different in the 3 groups (67%, 55%, and 62%, respectively), while a lower incidence of aGVHD was reported in patients treated with T-cell depleted haplo-HCT, compared with MUD and MMUD (II-IV aGVHD was 35% vs 44% vs 16%, respectively).

On the other hand, T cell replete haplo-HCT approaches are mainly based on PT-CY, pioneered by the John Hopkins group in the adult setting. [8, 34] This platform is now the most widely adopted strategy because it is cost-effective and easily replicated. In recent years, emerging evidence also supports the use of this platform in the pediatric population with hematological malignancies. [19,35]

Saglio et al. [15] retrospectively compared the outcome of 23 pediatric patients undergoing haplo-HCT with PT-CY for acute leukemia with patients undergoing HCT from MUD (n=41) and HLA mismatched unrelated donor (MMUD) (n=26) from a single institution. 5-yr OS, NRM and RI were not different for the three groups, confirming that haplo PT-CY is a suitable clinical option for pediatric patients. More recently, Srinivasan et al.[16] compared outcomes of haplo-HCT PT-CY with peripheral blood (n=26) to matched sibling donor (MSD) (n=31) and MUD HCT (n=47), both with BM as stem cell source. Results showed that haplo-HCT PT-CY with peripheral blood had comparable outcomes to BM MSD and MUD HCT. Hong et al. [17] compared the outcomes of children and adolescents with high-risk acute leukemia who underwent haplo-HCT PT-CY (n = 35) or MUD HCT (n = 45) after a busulfan-based myeloablative conditioning. No differences were observed in the main outcomes. In a subgroup analysis of patients with AML (haplo, n = 16; MUD, n = 16), the 3-yrs GRFS, LFS, and OS rates in haplo-HCT and MUD groups were 80.8% versus 61.9%, 87.1% versus 73.9%, and 93.8% versus 85.6%, respectively.

Here, we report the largest series of children with AML treated with haplo PT-CY reported to the EBMT registry. Our results are in line with the previous single center reports and confirmed the overall feasibility of the PT-CY approach in pediatric AML. Importantly, in our cohort Haplo HCT was associated with higher incidence of grade III-IV aGVHD and this could be related to the graft source itself, namely the content of CD3+ cells in the PBSC as well to the differences in the overall GVHD prophylaxis in the two group. Importantly MUD recipients received ATG which is a key factor associated with reduced risk of GVHD. Whenever the combination of ATG and PTCY could be considered in the pediatric setting deserves further investigation. Overall, no differences in pivotal outcome parameters were found between haplo PT-CY and MUD. The results were consistent across the different disease status when we checked for interaction between the disease status and the donor type. We are aware of the limitations of this study, namely the retrospective nature, the short follow-up, due to the recent use of PT-CY in this setting and the limited data on infection and immune reconstitution due to the registry based analysis. However we believe that our results are important and highlight the feasibility of this approach also in children. How the PTCY approach could be adopted also in the unrelated donor setting in the pediatric HCT deserves further investigation.

Eligibility criteria for HCT for each cooperative group are beyond the purpose of this multinational retrospective study. Nevertheless, eligibility for haplo-HCT may be either the same as for MUD or more restricted to higher risk patients only. Therefore, in case any unknown prognostic feature could not be adjusted within the matched pair analysis, the worst risk distribution would affect the outcome of the haplo PT-CY more than the MUD cohort. In the pair match analysis, the year of transplant was not considered as exact matching but using a propensity score. This resulted in a median year of transplant of 2017 and 2018 for MUD and Haplo respectively. Consequently, the median follow up was different in the two groups. To solve this issue and make the groups more comparable, we censored the outcomes at 2 years preventing us to provide results at a longer period to avoid imbalance between the groups.

Such a haplo platform may enlarge access to HCT to virtually all eligible pediatric patients with AML. Furthermore, the prompt availability and the flexibility of a family member may be crucial in the challenging HCT scheduling of rapidly evolving pediatric malignancies, such as high-risk AML. Albeit MUD-HCT remains the standard of care, our study confirmed in a large international analysis the comparable results of haplo-HCT with PT-CY and MD HCT, so that pediatric patients with AML who either lack a MD or cannot afford a MUD HCT, can be safely transplanted without delay.

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TABLES

Table 1. Patients and transplant characteristics

Variables	Modalities	N=516	MUD (N=420)	Haplo PT-CY (N=96)	p-value
Age at HCT	median [IQR]	8.5 [2.8-13.7]	7.7 [2.8-13.6]	9.8 [3-15.2]	0.03
Age at HCT	0-7	231 (44.8)	200 (47.6)	31 (32.3)	Not done
	7-12	107 (20.7)	82 (19.5)	25 (26)	
	12-18	178 (34.5)	138 (32.9)	40 (41.7)	
Disease status at HCT	CR1	366 (70.9)	296 (70.5)	70 (72.9)	0.63
	CR2	150 (29.1)	124 (29.5)	26 (27.1)	
Molecular remission	No	49 (15.6)	41 (15.9)	8 (14)	0.73
	Yes	266 (84.4)	217 (84.1)	49 (86)	
	missing	201	162	39	
Year of HCT	median[IQR]	2017 [2014-2019]	2016 [2014-2018]	2018 [2017-2020]	< 0.001
	missing	(2011-2021)	(2011-2021)	(2011-2021)	
Relation to donor	Parent			70 (83.3)	Not done
	Sibling			14 (16.7)	
	missing			12	
Donor age	median [IQR]	29.1 [23.8-36.3]	27.7 [23.3-34.2]	35.7 [29.5-42.7]	< 0.001
	missing	104	91	13	
Cell source	BM	330 (64)	267 (63.6)	63 (65.6)	0.71
	PB	186 (36)	153 (36.4)	33 (34.4)	
Patient sex	Female	242 (46.9)	197 (46.9)	45 (46.9)	0.99
	Male	274 (53.1)	223 (53.1)	51 (53.1)	
Female donor to male recipient	No	434 (84.1)	365 (86.9)	69 (71.9)	<0.001
	Yes	82 (15.9)	55 (13.1)	27 (28.1)	
Lansky or KPS	< 90	119 (23.1)	104 (24.8)	15 (15.6)	0.06

	≥ 90	397 (76.9)	316 (75.2)	81 (84.4)	
CMV-IgG match (donor-recipient)	Neg to Neg	120 (23.3)	112 (26.7)	8 (8.3)	< 0.001
	Neg to Pos	130 (25.2)	123 (29.3)	7 (7.3)	
	Pos to Neg	60 (11.6)	50 (11.9)	10 (10.4)	
	Pos to Pos	206 (39.9)	135 (32.1)	71 (74)	
Cytogenetic risk	Good	66 (14.9)	50 (13.6)	16 (21.3)	0.09
	Intermediate	199 (44.9)	163 (44.3)	36 (48)	
	Poor	178 (40.2)	155 (42.1)	23 (30.7)	
	missing	73	52	21	
GVHD prophylaxis	CSA+MTX based	289 (56)	288 (68.6)	1 (1)	Not done
	CSA based	71 (13.8)	66 (15.7)	5 (5.2)	
	CSA+MMF based	67 (13)	17 (4)	50 (52.1)	
	CSA+MMF+MTX based	12 (2.3)	9 (2.1)	3 (3.1)	
	Other	77 (14.9)	40 (9.5)	37 (38.5)	
Conditioning regimen	BuCyMel based	162 (31.4)	161 (38.3)	1 (1)	Not done
	BuCy based	131 (25.4)	121 (28.8)	10 (10.4)	
	BuFlu based	123 (23.8)	59 (14)	64 (66.7)	
	Treo based	88 (17.1)	70 (16.7)	18 (18.8)	
	Other combinations	12 (2.3)	9 (2.1)	3 (3.1)	

Abbreviations: MUD: matched unrelated donors; haplo: haploidentical; PT-CY: post-transplant cyclophosphamide, HCT: hematopoietic stem cell transplantation; BM: bone marrow; PB: peripheral blood; KPS: Karnofsky Performance status, CMV: cytomegalovirus; GVHD: graft versus host disease; CSA: cyclosporin; MTX: methotrexate, MMF: mycophenolate mofetile; Bu: busulfan, Flu: fludarabine; Cy: cyclophosphamide; Treo: treosulfan

Table 2. Patients and transplant characteristics in the matched pair cohort

Variables	Modalities	MUD (N=253)	Haplo PT-CY (N=95)
Age at HCT	median [IQR]	11.2 [4.9-14.6]	10 [3-15.4]
Age at HCT	0-7	87 (34.4)	31 (32.6)
	7-12	51 (20.2)	24 (25.3)
	12-18	115 (45.5)	40 (42.1)
Disease status at HCT	CR1	178 (70.4)	69 (72.6)
	CR2	75 (29.6)	26 (27.4)
Molecular remission	No	26 (16)	7 (12.5)
	Yes	136 (84)	49 (87.5)
	missing	91	39
Year of HCT	median [IQR]	2017 [2014-2019]	2018 [2017-2020]
Relation to donor	Parent		69 (83.1)
	Sibling		14 (16.9)
	missing		12
Donor age	median [IQR]	27 [23.2-34.2]	35.7 [29.5-42.8]
	(range)	(18.4-57.4)	(4.4-54.3)
	missing	48	13
Source of cells	BM	163 (64.4)	62 (65.3)
	PB	90 (35.6)	33 (34.7)
Patient sex	Female	123 (48.6)	44 (46.3)
	Male	130 (51.4)	51 (53.7)
Female to male	No	217 (85.8)	68 (71.6)
	Yes	36 (14.2)	27 (28.4)
Lansky or KPS	< 90	62 (24.5)	15 (15.8)
	≥90	191 (75.5)	80 (84.2)
CMV Ig G match (donor-recipient)	Neg to Neg	50 (19.8)	7 (7.4)
	Neg to Pos	64 (25.3)	7 (7.4)

	Pos to Neg	35 (13.8)	10 (10.5)
	Pos to Pos	104 (41.1)	71 (74.7)
Cytogenetic risk	Good	30 (13.7)	15 (20.3)
	Intermediate	123 (56.2)	36 (48.6)
	Poor	66 (30.1)	23 (31.1)
	missing	34	21
GVHD prophylaxis	CSA+MTX based	169 (66.8)	1 (1.1)
	CSA based	46 (18.2)	5 (5.3)
	CSA+MMF based	11 (4.3)	49 (51.6)
	CSA+MMF+MTX based	3 (1.2)	3 (3.2)
	Other	24 (9.5)	37 (38.9)
Conditionning regimen	BuCyMel based	89 (35.2)	1 (1.1)
	BuCy based	71 (28.1)	10 (10.5)
	BuFlu based	36 (14.2)	63 (66.3)
	Treo based	51 (20.2)	18 (18.9)
	Other combinations	6 (2.4)	3 (3.2)

Abbreviations: MUD: matched unrelated donors; haplo: haploidentical; PT-CY: post-transplant cyclophosphamide, HCT: hematopoietic stem cell transplantation; BM: bone marrow; PB: peripheral blood; KPS: Karnofsky Performance status, CMV: cytomegalovirus; CSA: cyclosporin; MTX: methotrexate, MMF: mycophenolate mofetile; Bu: busulfan; Flu: fludarabine; Cy: cyclophosphamide; Treo: treosulfan

Table 3. Survival outcomes after matched-pair analysis

	N=348	MUD (N=253)	Haplo (N=95)
Outcomes	**Estimation (95%CI)**	**Estimation (95%CI)**	**Estimation (95%CI)**
OS (2 y)	76.6 (71.2 - 81.2)	78.4 (72.2 - 83.4)	71.5 (59.1 - 80.7)
LFS (2 y)	71.8 (66.3 - 76.6)	72.7 (66.3 - 78.1)	69.5 (57.7 - 78.6)
RI (2 y)	19.4 (15.1 - 24.2)	19.3 (14.4 - 24.9)	19.5 (11.4 - 29.2)
NRM (2 y)	8.8 (6 - 12.2)	8 (5 - 11.9)	11 (5.2 - 19.1)
aGVHD II-IV (100 d)	30.8 (26 - 35.7)	28.7 (23.2 - 34.4)	36.7 (26.8 - 46.6)
aGVHD III-IV (100 d)	8.5 (5.8 - 11.8)	6.4 (3.8 - 9.9)	14.4 (8.1 - 22.5)
cGVHD (2 y)	19.5 (15 - 24.4)	18.5 (13.5 - 24.1)	22.4 (13.4 - 32.8)
cGVHD Ext (2 y)	8.2 (5.3 - 11.8)	8.6 (5.3 - 13)	6.6 (2.4 - 13.8)
GRFS (2 y)	59 (53 - 64.4)	60.7 (53.8 - 66.9)	54.5 (42.5 - 65)
neutrophil engraftment (60 d)	95.3 (92.3 - 97.1)	97.1 (93.9 - 98.6)	90.4 (82 - 95)
Platelet engraftment (180 d)	93.3 (89.5 - 95.8)	93.8 (89.1 - 96.4)	92.2 (82.6 - 96.6)

Abbreviations: MUD: matched unrelated donors; Haplo: haploidentical;

OS: overall survival; LFS: leukemia free survival; RI: relapse incidence; NRM: non relapse mortality; a: acute, c: chronic; GVHD: graft versus host disease; ext: extensive; GRFS: graft versus host free, relapse free survival

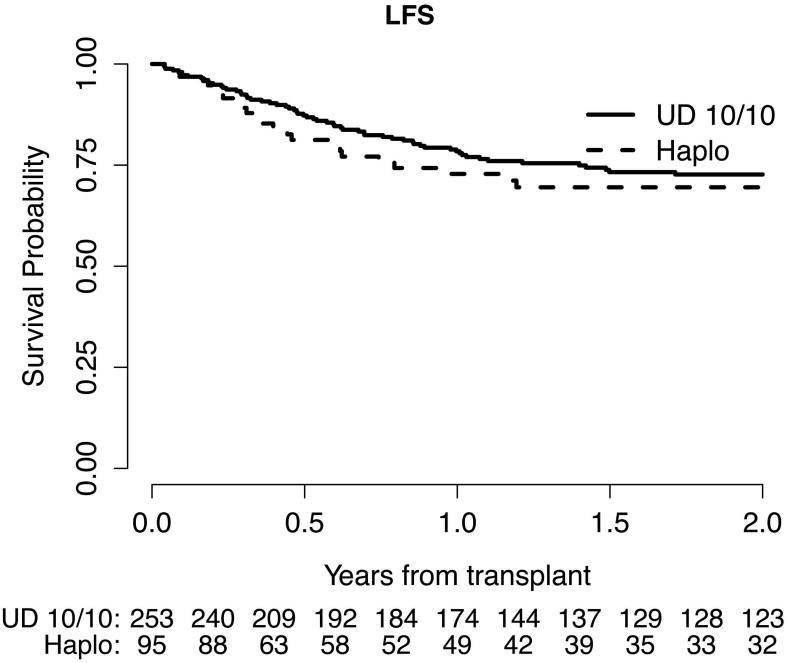
Table 4. Impact of donor type for outcomes censored at 2 years in the matched cohort

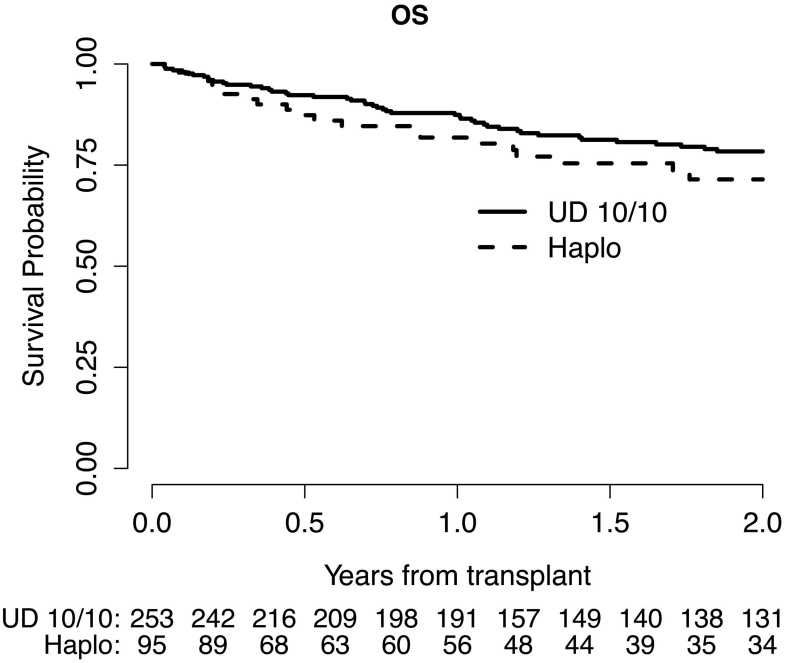
Outcome	HR (95%CI)	pvalue
OS	1.39 (0.84 -2.31)	0.19
LFS	1.22 (0.76 -1.95)	0.41
RI	1.14 (0.62 -2.08)	0.68
NRM	1.39 (0.66 -2.93)	0.39
aGVHD II-IV	1.26 (0.84 -1.89)	0.27
aGVHD III-IV	2.33 (1.18 -4.58)	**0.01**
cGVHD	1.81 (0.75 -4.37)	0.19
Ext cGVHD	1.01 (0.25 -4.03)	0.99
GRFS	1.38 (0.95 -2.02)	0.09

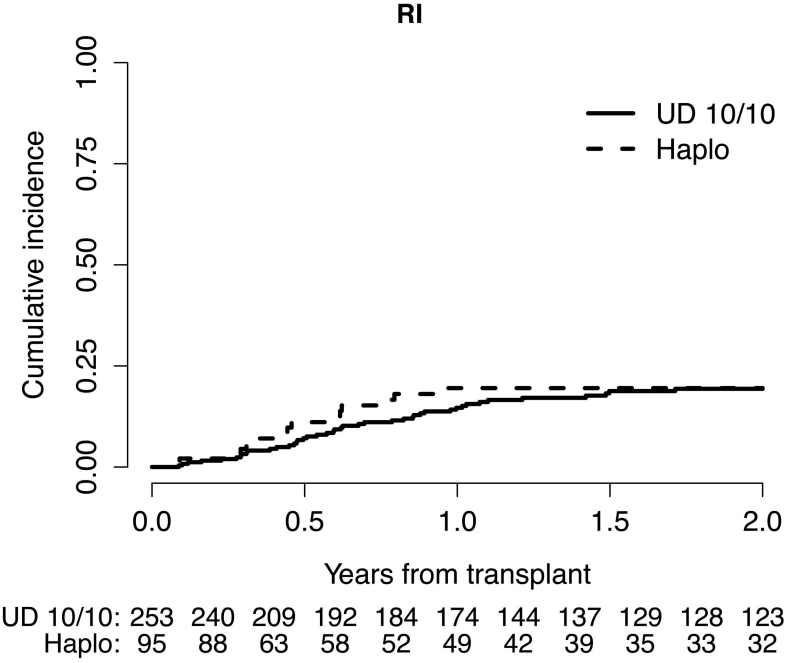
Abbreviations: MUD: matched unrelated donors; Haplo: haploidentical; OS: overall survival; LFS: leukemia free survival; RI: relapse incidence; NRM: non relapse mortality; a: acute, c: chronic; GVHD: graft versus host disease; ext: extensive; GRFS: graft versus host free, relapse free survival

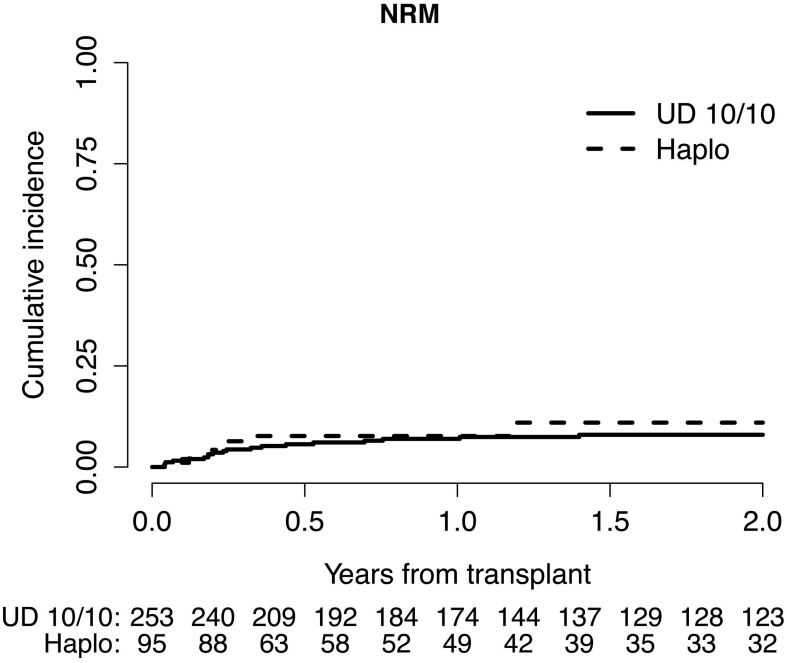
FIGURE LEGEND:

2 years LFS,OS,RI and NRM after MUD and Haplo HCT in children with AML after matched pair analysis.


LFS
Survival Probability
0.00
0.25
0.50
0.75
1.00
UD 10/10
Haplo
0.0
0.5
1.0
1.5
2.0
Years from transplant
UD 10/10: 253 240 209 192 184 174 144 137 129 128 123
Haplo: 95 88 63 58 52 49 42 39 35 33 32


OS
Survival Probability
0.00
0.25
0.50
0.75
1.00
UD 10/10
Haplo
0.0
0.5
1.0
1.5
2.0
Years from transplant
UD 10/10: 253 242 216 209 198 191 157 149 140 138 131
Haplo: 95 89 68 63 60 56 48 44 39 35 34


RI
Cumulative incidence
0.00
0.25
0.50
0.75
1.00
UD 10/10
Haplo
0.0
0.5
1.0
1.5
2.0
Years from transplant
UD 10/10: 253 240 209 192 184 174 144 137 129 128 123
Haplo: 95 88 63 58 52 49 42 39 35 33 32


NRM
Cumulative incidence
0.00
0.25
0.50
0.75
1.00
UD 10/10
Haplo
0.0
0.5
1.0
1.5
2.0
Years from transplant
UD 10/10: 253 240 209 192 184 174 144 137 129 128 123
Haplo: 95 88 63 58 52 49 42 39 35 33 32