

# Haploidentical vs sibling, unrelated, or cord blood hematopoietic cell transplantation for acute lymphoblastic leukemia

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The full-text version of this article contains a data supplement.

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### Key Points

- Haploidentical HCT is the preferred alternate donor approach for adults with ALL.
- Haploidentical transplantation had similar survival compared with fully HLA-matched donor HCT but with reduced GVHD.

The role of haploidentical hematopoietic cell transplantation (HCT) using posttransplant cyclophosphamide (PTCy) for acute lymphoblastic leukemia (ALL) is being defined. We performed a retrospective, multivariable analysis comparing outcomes of HCT approaches by donor for adults with ALL in remission. The primary objective was to compare overall survival (OS) among haploidentical HCTs using PTCy and HLA-matched sibling donor (MSD), 8/8 HLA-matched unrelated donor (MUD), 7/8 HLA-MUD, or umbilical cord blood (UCB) HCT. Comparing haploidentical HCT to MSD HCT, we found that OS, leukemia-free survival (LFS), nonrelapse mortality (NRM), relapse, and acute graft-versus-host disease (aGVHD) were not different but chronic GVHD (cGVHD) was higher in MSD HCT. Compared with MUD HCT, OS, LFS, and relapse were not different, but MUD HCT had increased NRM (hazard ratio [HR], 1.42;  $P = .02$ ), grade 3 to 4 aGVHD (HR, 1.59;  $P = .005$ ), and cGVHD. Compared with 7/8 UD HCT, LFS and relapse were not different, but 7/8 UD HCT had worse OS (HR, 1.38;  $P = .01$ ) and increased NRM (HR, 2.13;  $P \leq .001$ ), grade 3 to 4 aGVHD (HR, 1.86;  $P = .003$ ), and cGVHD (HR, 1.72;  $P \leq .001$ ). Compared with UCB HCT, late OS, late LFS, relapse, and cGVHD were not different but UCB HCT had worse early OS ( $\leq 18$  months; HR, 1.93;  $P < .001$ ), worse early LFS (HR, 1.40;  $P = .007$ ) and increased incidences of NRM (HR, 2.08;  $P < .001$ ) and grade 3 to 4 aGVHD (HR, 1.97;  $P < .001$ ). Haploidentical HCT using PTCy showed no difference in survival but less GVHD compared with traditional MSD and MUD HCT and is the preferred alternative donor HCT option for adults with ALL in complete remission.

## Introduction

Allogeneic hematopoietic cell transplantation (allo-HCT) is a curative therapy for acute lymphoblastic leukemia (ALL) and has been shown to be superior to intensive chemotherapy alone in some studies.<sup>1,2</sup> The UKALL XII/ECOG 2993 study compared an adult chemotherapy backbone or chemotherapy followed by myeloablative autologous HCT (auto-HCT) with myeloablative allo-HCT in patients with ALL age 15 to 59 years. An overall survival (OS) benefit was seen in patients with standard-risk ALL with a donor primarily because of higher rate of relapse in the no donor group than in the combined chemotherapy and auto-HCT groups.<sup>1</sup> A meta-analysis of 13 trials comparing allo-HCT to chemotherapy with or without auto-HCT concluded that the benefit of allo-HCT for patients with ALL in first complete remission (CR1) was limited to patients younger than age 35 years.<sup>3</sup> Recent studies have also shown that allo-HCT in CR1 yields outcomes similar to those in pediatric-inspired chemotherapy in patients who are minimal residual disease (MRD) negative but improves outcomes for patients who are MRD positive.<sup>4</sup> For these MRD-positive patients, who benefit most from allo-HCT in CR1, donor availability is especially important because haploidentical HCT or umbilical cord blood (UCB) HCT may shorten the time to allo-HCT and promote the higher cure rates observed with traditional fully HLA-matched donor allo-HCT.

The optimal donor for allo-HCT based on existing data seems to be a matched sibling donor (MSD) or an 8/8 HLA-matched unrelated donor (MUD) if an MSD is unavailable. A recently published study by the Center for International Blood and Marrow Transplant Research (CIBMTR) compared outcomes of traditional donor (MSD or MUD) HCT and 7/8 HLA-MUD HCT for adults with ALL. Compared with MSD HCT, MUD HCT yielded similar survival outcomes whereas the alternative 7/8 HLA-MUD HCT had inferior

survival.<sup>5</sup> For patients without a related or unrelated donor, haploidentical HCT using posttransplant cyclophosphamide (PTCy) for graft-versus-host disease (GVHD) prophylaxis is now a common alternative transplant modality with demonstrated efficacy in ALL.<sup>6-8</sup> In addition, despite having outcomes that are inferior to those for MSD and MUD HCT, 7/8 HLA-MUD and UCB HCT remain alternative graft sources for adult patients with ALL who do not have a fully HLA-matched donor.

Although comparative data to support the use of haploidentical HCT as a reasonable alternative to traditional MSD and MUD allo-HCT for acute myeloid leukemia (AML) are increasing,<sup>9-13</sup> comparative data for ALL are more limited. Recent retrospective, comparative studies using the European Society for Blood and Marrow Transplantation (EBMT) registry have found no differences in outcomes between haploidentical HCT using PTCy and MSD, MUD, and mismatched UD (MMUD) HCT.<sup>14,15</sup> The BMT-CTN 1101 study compared the results of parallel phase 2 studies of reduced-intensity conditioning (RIC) haploidentical HCT using PTCy and UCB HCT in lymphoma and acute leukemia. The study found no difference in the primary end point of progression-free survival at 2 years but found increased nonrelapse mortality (NRM) and decreased overall survival (OS) with UCB HCT compared with haploidentical HCT with PTCy.<sup>16</sup> Taken together, previous studies have shown no significant differences in OS when comparing haploidentical HCT to MSD, MUD, or MMUD HCT and a superior alternative donor approach among haploidentical HCT with PTCy, 7/8 HLA-matched UD HCT, and UCB HCT for adult ALL specifically has not been established.

This retrospective, multivariable study was designed to compare OS, leukemia-free survival (LFS), relapse, and NRM among adult patients with ALL undergoing postremission therapy with haploidentical HCT using PTCy compared with MSD HCT, MUD HCT, 7/8-HLA MUD HCT, or UCB HCT. We hypothesized that haploidentical HCT using PTCy would result in similar OS compared with MSD, MUD, and UCB HCT and superior OS compared with 7/8 HLA-MUD HCT in adults with ALL undergoing first allo-HCT in CR. Results from this study further define the role of haploidentical HCT for ALL in first or subsequent remissions.

## Patients and methods

### Patients

All patient data were generated from the CIBMTR patient registry. Eligible patients were age 18 years or older with a diagnosis of ALL in first, second, or third or greater CR undergoing first allo-HCT from 2013 through 2017. Patients must have had an allo-HCT from a haploidentical, HLA-MSD, 8/8 HLA-MUD, 7/8 HLA-MUD, or UCB donor.<sup>17</sup> Patients undergoing haploidentical HCT that did not use PTCy-based GVHD prophylaxis were excluded as were those receiving ex vivo T-cell depletion or CD34 selection. Also excluded were patients without consent to research, from embargoed centers, with no follow-up forms, alive with <3 months of follow-up, or receiving infrequently observed conditioning regimens. MRD testing methods and positivity were as reported from CIBMTR sites. MRD testing methods included flow cytometry (75%), molecular methods (76%), and cytogenetics (62%), with 74% of patients being evaluated with more than 1 method. Data on MRD testing methods was missing for 7% of patients. The study was approved by the Institutional Review Board of the National Marrow Donor Program.

### Study objectives

The primary objective was to compare OS after HCT among the following donor-transplant groups: haploidentical HCT using PTCy, MSD HCT, MUD HCT, 7/8 HLA-MUD HCT, and UCB HCT. Secondary objectives included comparing the LFS, relapse, NRM, grade 2 to 4 and grade 3 to 4 acute GVHD (aGVHD) rates,<sup>18</sup> and chronic GVHD (cGVHD) rates<sup>19</sup> among the groups. We also performed 2 planned sensitivity analyses restricting the analysis to myeloablative conditioning<sup>20</sup> with peripheral blood as a source for hematopoietic stem cells for non-cord blood donor types and to US centers only. We also determined causes of death in each group.

### Statistical analysis

This was a retrospective, 5-cohort comparative study from the CIBMTR. Patient-, disease-, and transplant-related factors were compared among the 5 transplant groups using  $\chi^2$  test for categorical variables and Mann-Whitney *U* test for continuous variables. The outcomes that were analyzed were OS, LFS, cumulative incidence (CI) of relapse, NRM CI, rate of aGVHD, and rate of cGVHD. OS was the time from transplantation to death as a result of any cause, with surviving patients censored at the last time they were reported alive. LFS was the time to leukemia relapse or death as a result of any cause, with surviving patients censored at the last time they were reported alive and were leukemia free. NRM was summarized by the CI estimate of death in CR with relapse as a competing risk. Relapse was summarized by the CI estimate with treatment-related mortality as a competing risk. Probabilities of OS and LFS were calculated by using the Kaplan-Meier estimator. CI curves were created to present relapse and NRM with time to relapse and time to NRM as competing risks.

To adjust for the differences in baseline characteristics, Cox proportional hazards regression was used to compare the main treatment groups. First, variables to be considered in the multivariable models were selected. Variables considered were donor type, recipient age, Karnofsky performance status, sex, HCT-CI score,<sup>21</sup> race, ALL lineage, Philadelphia chromosome (Ph)-*BCR-ABL1* status, cytogenetic risk, remission status, MRD status for CR1, time from diagnosis to HCT for CR1, conditioning intensity, donor-recipient sex match, donor-recipient cytomegalovirus (CMV) serostatus, year of transplant, and transplantation center. The assumption of proportional hazards for each factor in the Cox model was tested using time-dependent covariables. When the test indicated differential effects over time (nonproportional hazards), models were constructed that broke the posttransplant time course into 2 periods, using the maximized partial likelihood method to find the most appropriate breakpoint. The proportionality assumptions were further tested. A backward stepwise model selection approach was used to identify all significant risk factors. Each step of model building contained the main effect for treatment groups. Factors that were significant at a 5% level were kept in the final model. The potential interactions between main effect and all significant risk factors were tested. Adjusted probabilities of LFS and OS and adjusted CI estimates were generated from the final regression models stratified on treatment and weighted averages of covariable values using the pooled sample proportion as the weight function. These adjusted probabilities estimated likelihood of outcomes in populations with similar prognostic factors. With haploidentical HCT using PTCy as the baseline comparison group (independent testing, no multiple testing considered, no differences in patient characteristics adjusted, assuming all patients had at least a

**Table 1. Patient characteristics**

Characteristic	Donor and HCT group				UCB
	Haploidentical	Matched sibling	8/8 HLA-MUD	7/8 HLA-MUD	
No. of patients	393	1627	1646	230	305
No. of centers	92	206	181	90	79
Median follow-up, mo (range)	24 (3-67)	26 (3-72)	35 (3-74)	35 (3-64)	35 (3-64)
Median recipient age, y (range)	41 (18-74)	42 (18-75)	43 (18-77)	38 (18-70)	37 (18-70)
<b>Karnofsky performance status (%)</b>					
≥90	233 (59)	1046 (64)	995 (60)	163 (71)	196 (64)
<90	152 (39)	542 (33)	629 (38)	65 (28)	107 (35)
Missing	8 (2)	39 (2)	22 (1)	2 (<1)	2 (<1)
No. of male recipients	214 (54)	969 (60)	976 (59)	134 (58)	176 (58)
<b>HCT-CI score</b>					
0	81 (21)	592 (36)	405 (25)	53 (23)	89 (29)
1	57 (15)	221 (14)	224 (14)	35 (15)	42 (14)
2	61 (16)	228 (14)	266 (16)	37 (16)	46 (15)
3+	194 (49)	552 (34)	745 (45)	104 (45)	125 (41)
Missing	0	34 (2)	6 (<1)	1 (<1)	3 (<1)
<b>Race/ethnicity*</b>					
Hispanic White	87 (22)	246 (15)	136 (8)	42 (18)	64 (21)
Non-Hispanic White	170 (43)	846 (52)	1226 (74)	113 (49)	150 (49)
Black	59 (15)	74 (5)	53 (3)	19 (8)	27 (9)
Asian	22 (6)	111 (7)	64 (4)	10 (4)	22 (7)
Other/not specified	55 (14)	350 (22)	167 (10)	46 (20)	42 (14)
<b>Immunophenotype</b>					
T cell	25 (6)	201 (12)	186 (11)	27 (12)	36 (12)
B cell	330 (84)	1316 (81)	1319 (80)	185 (80)	246 (81)
Not specified	38 (10)	110 (7)	141 (9)	18 (8)	23 (8)
<b>Cytogenetic risk score†</b>					
Normal	91 (23)	320 (20)	335 (20)	52 (23)	63 (21)
Poor	222 (56)	750 (46)	855 (52)	101 (44)	154 (50)
Missing/not tested/other	80 (21)	557 (34)	456 (28)	77 (33)	88 (29)
Ph/ <i>BCR-ABL1</i> -positive	152 (46)	562 (43)	614 (47)	80 (43)	122 (50)
<b>Remission status</b>					
CR1, MRD positive	112 (28)	513 (32)	509 (31)	58 (25)	78 (26)
CR1, MRD negative	143 (36)	644 (40)	697 (42)	85 (37)	124 (41)
CR1, MRD missing	14 (4)	145 (9)	59 (4)	6 (3)	10 (3)
CR2	105 (27)	296 (18)	334 (20)	62 (27)	74 (24)
≥CR3	19 (5)	29 (2)	47 (3)	19 (8)	19 (6)
<b>Time from diagnosis to HCT (CR1 only) (mo)</b>					
0-5	130 (48)	842 (65)	744 (59)	56 (38)	93 (44)
6-11	115 (43)	388 (30)	463 (37)	81 (54)	102 (48)
≥12	24 (9)	72 (6)	58 (5)	12 (8)	17 (8)
<b>Conditioning regimen</b>					
MAC, TBI-based	163 (41)	984 (60)	950 (58)	139 (60)	217 (71)
MAC, chemotherapy-based	63 (16)	323 (20)	312 (19)	51 (22)	11 (4)
RIC/NMA	167 (42)	316 (19)	383 (23)	39 (17)	76 (25)

*BCR-ABL*, breakpoint cluster region-Abelson murine leukemia; CMV, cytomegalovirus; CNI, calcineurin inhibitor; MAC, myeloablative conditioning; MMF, mycophenolate mofetil; MTX, methotrexate; NA, not applicable; NMA, non-myeloablative.

\*Other/not specified: Native American (n = 30), Pacific Islander (n = 20), non-resident of the United States (n = 291), not specified (n = 156), Hispanic, excluding White Hispanic (n = 213).

†CIBMTR cytogenetics criteria definition: Poor: Ph<sup>+</sup>/t(9:22)/*BCR-ABL1*, t(4:11), 11q23/MLL/KMT2A, hypodiploid (<45), t(8:14), complex (≥3 abnormalities), iAMP21; normal: without any abnormality; other: abnormality count of 1 or 2 abnormalities.

**Table 1. (continued)**

Characteristic	Donor and HCT group				
	Haploidentical	Matched sibling	8/8 HLA-MUD	7/8 HLA-MUD	UCB
Missing	0	4 (<1)	1 (<1)	1 (<1)	1 (<1)
<b>Donor/recipient sex</b>					
Female donor/male recipient	82 (21)	415 (26)	244 (15)	42 (18)	161 (53)
other donor/recipient	311 (79)	1212 (74)	1396 (85)	188 (82)	137 (45)
Missing	0	0	6 (<1)	0	7 (2)
<b>Donor/recipient CMV serostatus</b>					
+/+	206 (52)	859 (53)	506 (31)	90 (39)	0
+/-	31 (8)	144 (9)	197 (12)	25 (11)	0
-/+	83 (21)	287 (18)	553 (34)	64 (28)	0
-/-	72 (18)	306 (19)	382 (23)	50 (22)	0
UCB-/recipient+	0	0	0	0	200 (66)
UCB-/recipient-	0	0	0	0	100 (33)
Missing	1 (<1)	31 (2)	8 (<1)	1 (<1)	5 (2)
Median donor age, y (range)	35 (10-74)	41 (9-75)	28 (18-60)	31 (19-60)	NA
<b>Graft source</b>					
Bone marrow	160 (41)	230 (14)	316 (19)	67 (29)	-
Peripheral blood	233 (59)	1397 (86)	1330 (81)	163 (71)	-
<b>GVHD prophylaxis</b>					
CNI + MTX ± others	0	1107 (68)	1165 (71)	162 (70)	7 (2)
CNI + MMF ± others	0	236 (15)	191 (12)	18 (8)	265 (87)
CNI + others	0	118 (7)	141 (9)	13 (6)	6 (2)
CNI alone	0	66 (4)	58 (4)	5 (2)	14 (5)
PTCy + CNI ± MMF	393 (100)	75 (5)	73 (4)	29 (13)	2 (<1)
Other prophylaxis	0	17 (1)	13 (<1)	2 (<1)	10 (3)
Missing	0	8 (<1)	5 (<1)	1 (<1)	1 (<1)
<b>In vivo T-cell depletion</b>					
Antithymocyte globulin	5 (1)	76 (5)	561 (34)	116 (50)	39 (13)
Alemtuzumab	0	33 (2)	62 (4)	6 (3)	0
None	388 (99)	1505 (93)	1010 (61)	105 (46)	265 (87)
Missing	0	13 (<1)	13 (<1)	3 (1)	1 (<1)

*BCR-ABL*, breakpoint cluster region-Abelson murine leukemia; CMV, cytomegalovirus; CNI, calcineurin inhibitor; MAC, myeloablative conditioning; MMF, mycophenolate mofetil; MTX, methotrexate; NA, not applicable; NMA, non-myeloablative.

\*Other/not specified: Native American (n = 30), Pacific Islander (n = 20), non-resident of the United States (n = 291), not specified (n = 156), Hispanic, excluding White Hispanic (n = 213).

†CIBMTR cytogenetics criteria definition: Poor: Ph<sup>+</sup>/t(9:22)/*BCR-ABL1*, t(4:11), 11q23/MLL/KMT2A, hypodiploid (<45), t(8:14), complex (≥3 abnormalities), iAMP21; normal: without any abnormality; other: abnormality count of 1 or 2 abnormalities.

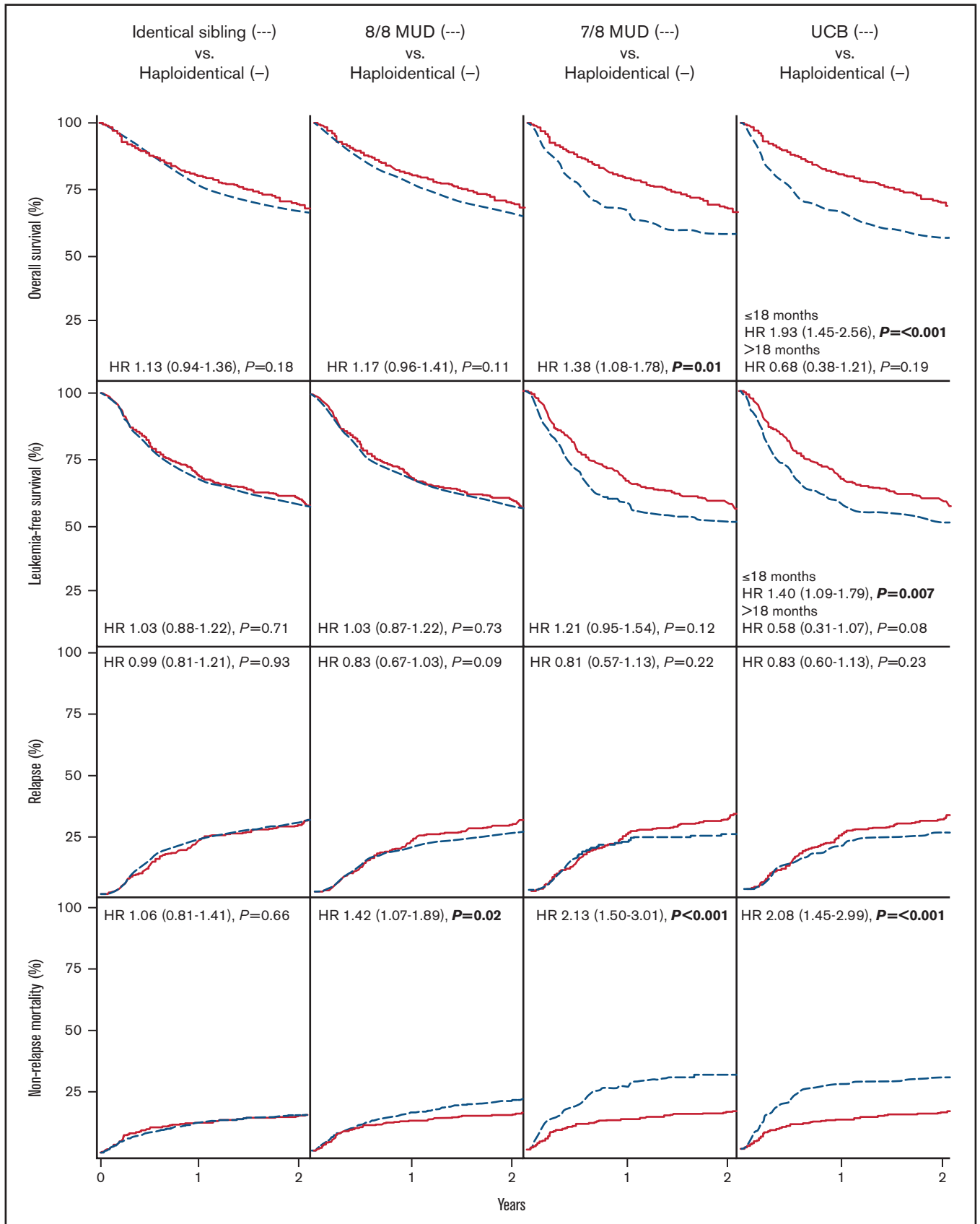
2-year follow-up), the power test for 2-year OS probability was based on a two-sided test with a significance level of 5%: haploidentical HCT using PTCy vs (1) MSD HCT, 80% power to detect at least a difference of 8%; (2) MUD HCT, 80% power to detect at least a difference of 8%; (3) 7/8 HLA-MUD HCT, 80% power to detect at least a difference of 11%; and (4) UCB HCT, 80% power to detect at least difference of 10%.

## Results

### Patients

Between 2013 and 2017, a total of 4201 patients in 5 HCT cohorts were eligible: 393 haploidentical HCT using PTCy, 1627 MSD HCT, 1646 MUD HCT, 230 7/8 HLA-matched UD HCT, and

305 UCB HCT. Cohorts were well matched for age, sex, Karnofsky performance status, HCT-CI, immunophenotype, cytogenetic risk, Ph-*BCR-ABL1* status, disease status, MRD status at transplantation, and recipient CMV serostatus. Notable differences between groups included race, time from diagnosis to HCT (CR1 only), conditioning regimen intensity, donor age, graft source for non-cord blood (peripheral blood or bone marrow), GVHD prophylaxis modality, and the use of in vivo T-cell depletion. PTCy-based GVHD prophylaxis was used in 5% of MSD HCT, 4% of MUD HCT, and 13% of 7/8 HLA-MUD HCT. Compared with other groups, haploidentical HCT using PTCy had the lowest percentage of non-Hispanic White patients (43% vs 49%-74%), was more likely to use RIC (42% vs 17%-25%), and was more likely to use bone marrow as the graft source (41% vs 14%-29%) (Table 1).



**Figure 1.** OS, LFS, CI of relapse, and CI of NRM comparing haploidentical HCT with posttransplant cyclophosphamide to matched sibling, 8/8 HLA-MUD, 7/8 HLA-MUD, or UCB HCT.

**Table 2. Multivariable analysis for HLA-MSD HCT vs haploidentical HCT, 2013-2017**

Covariate	No.	HR	95% Confidence interval	P
<b>OS</b>				
Main effect				
Haploidentical HCT	393	Reference		
MSD HCT	1627	1.13	0.94-1.36	.18
Remission status				
CR1	1571	Reference		
CR2+	449	1.86	1.58-2.19	<.001
Age (y)				
18-29	572	Reference		
30-39	367	0.97	0.77-1.22	.78
40-49	432	1.30	1.05-1.60	.02
50-59	417	1.49	1.21-1.85	<.001
60-69	232	2.07	1.63-2.63	<.001
Donor/recipient sex match				
Other than F/M	1523	Reference		
F/M	497	1.29	1.10-1.51	.002
Ph-BCR-ABL1 status				
Negative	932	Reference		
Positive	714	0.78	0.66-0.92	.003
T-cell-ALL/unspecified subtype	374	1.02	0.84-1.24	.83
Donor/recipient CMV serostatus				
+/+	1065	Reference		
+/-	175	0.81	0.62-1.05	.11
-/+	370	0.76	0.62-0.93	.007
-/-	378	0.84	0.69-1.01	.07
<b>LFS</b>				
Main effect				
Haploidentical HCT	381	Reference		
MSD HCT	1583	1.03	0.88-1.22	.71
Disease status				
CR1	1528	Reference		
CR2+	436	1.93	1.67-2.23	<.001
Conditioning regimen				
MAC-TBI	1116	Reference		
MAC-chemotherapy	376	1.35	1.15-1.60	<.001
RIC/NMA	470	1.50	1.28-1.76	<.001
<b>NRM</b>				
Main effect				
Haploidentical HCT	381	Reference		
MSD HCT	1583	1.06	0.81-1.41	.66
Remission status				
CR1	1528	Reference		
CR2+	436	1.52	1.17-1.98	.002
Age (y)				
18-29	553	Reference		
30-39	353	0.66	0.44-0.99	.04
40-49	422	1.19	0.86-1.65	.28
50-59	411	1.59	1.17-2.16	.003

F, female; M, male.

**Table 2. (continued)**

Covariate	No.	HR	95% Confidence interval	P
60-69	225	2.10	1.49-2.96	<.001
Donor/recipient sex match				
Other than F/M	1479	Reference		
F/M	485	1.54	1.22-1.94	<.001
<b>Relapse</b>				
Main effect				
Haploidentical HCT	381	Reference		
MSD HCT	1583	0.99	0.81-1.21	.93
Remission status				
CR1	1528	Reference		
CR2+	436	2.25	1.89-2.68	<.001
Conditioning regimen				
MAC-TBI	1116	Reference		
MAC-chemotherapy	376	1.40	1.14-1.72	.001
RIC/NMA	470	1.53	1.26-1.87	<.001
<b>aGVHD, grade 2-4</b>				
Main effect				
Haploidentical HCT	376	Reference		
MSD HCT	1545	0.92	0.77-1.11	.40
<b>aGVHD, grade 3-4</b>				
Main effect				
Haploidentical HCT	376	Reference		
MSD HCT	1545	1.09	0.79-1.50	.59
<b>cGVHD</b>				
MSD vs haploidentical HCT for donor/recipient sex match, other		1.37	1.12-1.69	.003
MSD vs haploidentical HCT for donor/recipient sex match, F/M		2.59	1.68-3.99	<.001
Age (y)				.002
18-29	563	Reference		
30-39	361	1.13	0.93-1.37	.24
40-49	428	1.37	1.14-1.64	<.001
50-59	413	1.17	0.95-1.43	.14
60-69	228	1.57	1.21-2.03	<.001
Race/ethnicity				
White Hispanic	333	Reference		
White non-Hispanic	1006	0.75	0.63-0.89	.001
Black	132	0.93	0.70-1.23	.61
Asian	130	0.79	0.59-1.07	.13
Other/not specified	392	0.66	0.53-0.82	<.001
Donor/recipient sex match				
Other than F/M	1501	Reference		
F/M	492	0.73	0.47-1.14	.17
Conditioning regimen				
MAC-TBI	1132	Reference		
MAC-chemotherapy	380	0.94	0.79-1.11	.46
RIC/NMA	478	0.74	0.61-0.90	.002

F, female; M, male.



**Table 3. Multivariable analysis for 8/8 HLA-MUD HCT vs haploidentical HCT, 2013-2017**

Covariate	No.	HR	95% Confidence interval	P
<b>OS</b>				
Main effect				
Haploidentical HCT	393	Reference		
MUD HCT	1646	1.17	0.96-1.41	.11
Remission status				
CR1	1534	Reference		
CR2+	505	1.79	1.53-2.10	<.001
Age (y)				
18-29	545	Reference		<.001
30-39	364	1.03	0.81-1.30	.82
40-49	391	1.38	1.11-1.71	.004
50-59	382	1.55	1.24-1.93	<.001
60-69	357	1.85	1.48-2.31	<.001
Race/ethnicity				
White Hispanic	223	Reference		
White non-Hispanic	1396	0.95	0.75-1.21	.68
Black	112	1.33	0.94-1.87	.11
Asian	86	0.44	0.26-0.75	.002
Other/not specified	222	1.02	0.74-1.39	.92
HCT-CI				
0	486	Reference		.01
1	281	1.01	0.79-1.30	.91
2	327	1.03	0.81-1.30	.84
3+	939	1.25	1.04-1.50	.02
Ph-BCR-ABL1 status				
Negative	883	Reference		
Positive	766	0.82	0.70-0.96	.02
T-ALL/unspecified subtype	390	1.03	0.85-1.24	.77
<b>LFS</b>				
Main effect				
Haploidentical HCT	381	Reference		
MUD HCT	1618	1.03	0.87-1.22	.73
Remission status				
CR1	1509	Reference		
CR2+	490	1.74	1.51-1.99	<.001
Race/ethnicity				
White Hispanic	217	Reference		
White non-Hispanic	1379	0.97	0.78-1.19	.76
Black	105	1.33	0.98-1.82	.07
Asian	84	0.57	0.37-0.87	.01
Other/not specified	214	0.94	0.71-1.24	.67
Conditioning regimen				
MAC-TBI	1097	Reference		
MAC-chemotherapy	363	1.46	1.24-1.73	<.001
RIC/NMA	539	1.61	1.39-1.87	<.001
<b>NRM</b>				
Main effect				
Haploidentical HCT	381	Reference		

**Table 3. (continued)**

Covariate	No.	HR	95% Confidence interval	P
MUD HCT	1618	1.42	1.07-1.89	.02
Remission status				
CR1	1509	Reference		
CR2+	490	1.33	1.06-1.67	.01
Age (y)				
18-29	539	Reference		<.001
30-39	356	0.86	0.62-1.20	.37
40-49	382	1.30	0.97-1.76	.08
50-59	372	1.61	1.20-2.15	.001
60-69	350	1.82	1.36-2.44	<.001
Race/ethnicity				
White Hispanic	217	Reference		
White non-Hispanic	1379	0.79	0.58-1.09	.15
Black	105	1.04	0.63-1.73	.87
Asian	84	0.35	0.16-0.74	.006
Other/not specified	214	0.98	0.66-1.47	.93
<b>Relapse</b>				
Main effect				
Haploidentical HCT	381	Reference		
MUD HCT	1618	0.83	0.67-1.03	.09
Remission status				
CR1	1509	Reference		
CR2+	490	2.20	1.84-2.64	<.001
Sex				
Male	1168	Reference		
Female	831	0.81	0.68-0.97	.02
Race/ethnicity				
White Hispanic	217	Reference		
White non-Hispanic	1379	1.04	0.78-1.39	.77
Black	105	1.59	1.06-2.37	.02
Asian	84	0.75	0.44-1.26	.27
Other/not specified	214	0.88	0.60-1.29	.52
Conditioning regimen				
MAC-TBI	1097	Reference		
MAC-chemotherapy	363	1.57	1.25-1.98	<.001
RIC/NMA	539	1.83	1.50-2.23	<.001
<b>aGVHD, grade 2-4</b>				
Main effect				
Haploidentical HCT	376	Reference		
MUD HCT	1553	1.17	0.98-1.41	.09
Conditioning regimen				
MAC-TBI	1042	Reference		
MAC-chemotherapy	367	0.86	0.72-1.04	.11
RIC/NMA	519	0.81	0.68-0.95	.01
<b>aGVHD, grade 3-4</b>				
Main effect				
Haploidentical HCT	376	Reference		
MUD HCT	1553	1.59	1.15-2.20	.005

**Table 3. (continued)**

Covariate	No.	HR	95% Confidence interval	P
<b>Race/ethnicity</b>				
White Hispanic	217	Reference		
White non-Hispanic	1318	0.65	0.47-0.90	.009
Black	109	0.90	0.53-1.53	.69
Asian	80	0.29	0.12-0.68	.005
Other/not specified	205	0.67	0.43-1.06	.08
<b>cGVHD</b>				
MUD vs haploidentical for donor/recipient sex match, other		1.38	1.14-1.68	.001
MUD vs haploidentical for donor/recipient sex match, F/M		2.91	1.87-4.52	<.001
<b>Remission status</b>				
CR1	1528	Reference		
CR2+	501	0.81	0.69-0.95	.009
<b>Donor/recipient sex match</b>				
Other than F/M	1707	Reference		
F/M	322	0.69	0.44-1.08	.10

**OS and LFS**

In multivariable analysis, compared with haploidentical HCT, MSD HCT and MUD HCT had similar OS (hazard ratio [HR], 1.13;  $P = .18$  and HR, 1.17;  $P = .11$ , respectively) and LFS (HR, 1.03 [ $P = .71$ ] and HR, 1.03 [ $P = .73$ ], respectively). In contrast, 7/8 HLA-MUD HCT had inferior OS and similar LFS when compared with haploidentical HCT (OS: HR, 1.38 [ $P = .01$ ]; LFS: HR, 1.21 [ $P = .12$ ]). UCB HCT had inferior OS before 18 months (HR, 1.93;  $P \leq .001$ ) and similar OS after 18 months (HR, 0.68;  $P = .19$ ) when compared with haploidentical HCT. In addition, LFS before 18 months was inferior to UCB HCT (HR, 1.40;  $P = .007$ ) and was similar after 18 months (HR, 0.58;  $P = .08$ ). Other multivariable factors associated with decreased OS included HCT in CR2+, older age, female donor to male recipient, Ph-BCR-ABL1 negativity, and CMV-seronegative donor to CMV-seropositive recipient for MSD HCT vs haploidentical HCT; CR2+, older age, non-Asian race, HCT-CI 3+, and Ph-BCR-ABL1 negativity for MUD HCT vs haploidentical HCT; CR2+ for 7/8 HLA-MUD HCT vs haploidentical HCT; and CR2+ and myeloablative chemotherapy (vs myeloablative total body irradiation [TBI]) for UCB HCT vs haploidentical HCT. Multivariable survival outcomes are summarized in Tables 2-5 and Figure 1. Univariable outcomes are summarized in supplemental Table 3.

**Relapse and NRM**

In multivariable analysis, MSD HCT had similar relapse (HR, 0.99;  $P = .93$ ) and NRM (HR, 1.06;  $P = .66$ ) compared with haploidentical HCT. Compared with haploidentical HCT, relapse was not significantly different with MUD HCT (HR, 0.83;  $P = .09$ ), 7/8 HLA-MUD HCT (HR, 0.81;  $P = .22$ ), or UCB HCT (HR, 0.83;  $P = .23$ ). NRM, however, was significantly higher with MUD HCT (HR, 1.42;  $P = .02$ ), 7/8 HLA-MUD HCT (HR, 2.13;  $P \leq .001$ ), or UCB HCT (HR, 2.08;  $P \leq .001$ ) compared with haploidentical HCT. Notably, myeloablative conditioning using TBI significantly reduced the risk of relapse across all donor HCT cohorts. Multivariable relapse and NRM analyses are summarized in Tables 2-5 and Figure 1. Univariable analyses are summarized in supplemental Table 3.

**GVHD**

Multivariable analysis revealed either reduced or similar rates of severe aGVHD and cGVHD with haploidentical HCT using PTCy relative to other HCT cohorts. Compared with haploidentical HCT, MSD HCT had similar CIs of grade 2 to 4 and grade 3 to 4 aGVHD (HR, 0.92 [ $P = .40$ ] and HR, 1.09 [ $P = .59$ ], respectively) but increased CI of cGVHD (HR, 2.59;  $P < .001$  for female-male donor-recipient sex match; HR 1.37;  $P = .003$  for other donor-recipient sex match). MUD HCT had a similar CI of grade 2 to 4 aGVHD (HR, 1.17;  $P = .09$ ), an increased CI of grade 3 to 4 aGVHD (HR, 1.59;  $P = .005$ ), and an increased CI of cGVHD (HR, 1.38;  $P = .001$ ). 7/8 HLA-MUD HCT had an increased CI of grade 2 to 4 aGVHD (HR, 1.33;  $P = .04$ ), grade 3 to 4 aGVHD (HR, 1.86;  $P = .003$ ), and cGVHD (HR, 1.72;  $P < .001$ ). UCB HCT was associated with an increased CI of grade 2 to 4 and grade 3 to 4 aGVHD (HR, 1.83 [ $P < .001$ ] and HR, 1.97; [ $P < .001$ ], respectively) with a similar CI of cGVHD (HR, 1.13;  $P = .38$ ). Multivariable GVHD analyses are summarized in Tables 2-5.

**Causes of death**

Death from ALL was more common with haploidentical HCT (48%) and HLA-identical sibling HCT (52%) compared with other HCT cohorts (31%-38%). Death from GVHD accounted for 5% of deaths after haploidentical HCT compared with 12% to 24% in other HCT cohorts. Similar rates of death from infection were observed when comparing haploidentical HCT (21%) to other HCT cohorts (17%-23%). Other causes of death were also similar among the cohorts (detailed summary in Table 6).

**Sensitivity analyses**

To address 2 potential sources of bias, we performed 2 sensitivity analyses for OS, LFS, relapse, and NRM, restricting the study population to either the most common modalities of myeloablative conditioning with peripheral blood as a source of hematopoietic stem cells or to US centers for better completion of follow-up at 2 years. When restricted to myeloablative conditioning and peripheral blood

**Table 4. Multivariable analysis for 7/8 HLA-MUD HCT vs haploidentical HCT, 2013-2017**

Covariate	No.	HR	95% Confidence interval	P
<b>OS</b>				
Main effect				
Haploidentical HCT	393	Reference		
7/8 HLA-MUD HCT	230	1.38	1.08-1.78	.01
Remission status				
CR1	418	Reference		
CR2+	205	1.82	1.41-2.34	<.001
<b>LFS</b>				
Main effect				
Haploidentical HCT	381	Reference		
7/8 HLA-MUD	227	1.21	0.95-1.54	.12
Remission status				
CR1	414	Reference		
CR2+	194	1.84	1.46-2.33	<.001
Race/ethnicity				
White Hispanic	124	Reference		
White non-Hispanic	277	0.95	0.71-1.28	.73
Black	75	1.33	0.92-1.94	.13
Asian	32	0.50	0.25-0.97	.04
Other/not specified	100	0.70	0.48-1.03	.07
Conditioning regimen				
MAC-TBI	295	Reference		
MAC-chemotherapy	111	1.29	0.94-1.75	.11
RIC/NMA	201	1.46	1.12-1.89	.005
<b>NRM</b>				
Main effect				
Haploidentical HCT	381	Reference		
7/8 HLA-MUD HCT	227	2.13	1.50-3.01	<.001
Donor/recipient CMV serostatus				
+/+	287	Reference		
+/-	55	0.40	0.18-0.86	.02
-/+	143	0.78	0.51-1.19	.25
-/-	121	0.56	0.34-0.92	.02
<b>Relapse</b>				
Main effect				
Haploidentical HCT	381	Reference		
7/8 HLA-MUD HCT	227	0.81	0.57-1.13	.22
Remission status				
CR1	414	Reference		
CR2+	194	2.39	1.76-3.25	<.001
Race/ethnicity				
White Hispanic	124	Reference		
White non-Hispanic	277	0.94	0.64-1.39	.76
Black	75	1.24	0.76-2.02	.38
Asian	32	0.36	0.14-0.93	.03
Other/not specified	100	0.58	0.34-0.99	.05
Conditioning regimen				
MAC-TBI	295	Reference		

**Table 4. (continued)**

Covariate	No.	HR	95% Confidence interval	P
MAC-chemotherapy	111	1.60	1.05-2.44	.03
RIC/NMA	201	2.09	1.49-2.95	<.001
<b>aGVHD, grade 2-4</b>				
Main effect				
Haploidentical HCT	376	Reference		
7/8 HLA-MUD HCT	216	1.33	1.02-1.73	.04
Conditioning regimen				
MAC-TBI	288	Reference		
MAC-chemotherapy	107	0.68	0.47-0.98	.04
RIC/NMA	196	0.68	0.51-0.92	.01
<b>aGVHD, grade 3-4</b>				
Main effect				
Haploidentical HCT	376	Reference		
7/8 HLA-MUD HCT	216	1.86	1.23-2.80	.003
<b>cGVHD</b>				
Main effect				
Haploidentical HCT	393	Reference		
7/8 HLA-MUD HCT	230	1.72	1.34-2.20	<.001

stem cell source, outcomes were similar to those for the full population except that decreased OS with 7/8 HLA-MUD compared with haploidentical HCT was no longer statistically significant (HR, 1.39;  $P = .07$ ; supplemental Tables 1, 4, 6-9; supplemental Figures 1-4). When restricted to US centers only, outcomes were also similar except there was a decreased risk of relapse (HR, 0.76;  $P = .02$ ) but inferior OS (HR, 1.23; 95% confidence interval, 1.00-1.50;  $P = .05$ ) with MUD compared with haploidentical HCT (supplemental Tables 2, 5, 10-13; supplemental Figures 1-4).

## Discussion

Haploidentical HCT is a growing allo-HCT modality for ALL that has expanded allo-HCT to patients without traditional HLA-matched related or unrelated donors, especially those of mixed race or ethnicity. The choice of alternative donors for allo-HCT in ALL is an area of ongoing research, debate, and clinical interest. In addition, the relative benefits of haploidentical HCT compared with traditional MSDs and MUDs is just being defined. In this study, we demonstrated that haploidentical HCT using PTCy resulted in OS similar to that in traditional MSD and MUD allo-HCT but with less GVHD. In addition, we found superior OS compared with alternative 7/8 HLA-MUD and UCB HCT. The superior survival seen with haploidentical HCT using PTCy compared with 7/8 HLA-MUD HCT and UCB HCT was likely due to reduced NRM related to reduced GVHD with haploidentical HCT. Notably, rates of infection were similar among the 5 cohorts, suggesting that delayed immune reconstitution with haploidentical HCT in the adult ALL population did not translate into increased infection-related mortality.

Previous smaller retrospective studies comparing haploidentical HCT to MSD, MUD, and MMUD HCT found no differences in disease-free survival, relapse, NRM, aGVHD, or cGVHD. Recently, Shem-Tov et al<sup>14</sup> performed a retrospective multi-institution

comparison of 136 ALL patients undergoing haploidentical HCT with 809 patients with ALL receiving MUD HCT and 289 patients with ALL receiving 9/10 HLA-MUD HCT. This smaller study found no differences in OS, LFS, relapse, NRM, aGVHD, or cGVHD among the groups.<sup>14</sup> Similarly, a larger study comparing 487 haploidentical HCTs to 974 MUD HCTs for ALL found no difference in any outcome, including aGVHD and cGVHD.<sup>15</sup> Our study expands on and contrasts these studies with a large contemporary population that showed significant differences in major outcomes between haploidentical HCT using PTCy to all other major donor sources. This study helps clarify the role of haploidentical HCT in adult ALL and expands our knowledge of the expected benefits of haploidentical HCT relative to other donor HCT approaches. Importantly, our study supports haploidentical HCT with PTCy as the preferred HCT approach for patients who do not have an MSD or MUD.

Similar to previous studies,<sup>22-25</sup> our results show that myeloablative conditioning using TBI compared with myeloablative chemotherapy or RIC/non-myeloablative conditioning significantly reduced the risk of relapse and improved LFS across all donor HCT cohorts. The recently published Phase III FORUM study randomly assigned 417 children and young adults ages 4 to 21 years with ALL to either myeloablative TBI-based or myeloablative chemotherapy-based conditioning before MSD, MUD, or MMUD allo-HCT. Patients in the TBI arm had improved OS, improved event-free survival, less relapse, and improved NRM.<sup>23</sup> In adults with ALL, a retrospective EBMT registry study comparing TBI-based to chemotherapy-myeloablative conditioning for MSD, MUD, or MMUD allo-HCT found better OS, LFS, and relapse incidence with TBI-based conditioning,<sup>24</sup> although the OS benefit in adults has not been seen across all retrospective studies.<sup>22,25</sup> In this study, the benefit of myeloablative conditioning using TBI on reducing relapse improved OS only in haploidentical HCT and UCB HCT comparisons, suggesting that these modalities may derive more benefit from TBI. Overall, our study supports

**Table 5. Multivariable analysis for UCB HCT vs haploidentical HCT, 2013-2017**

Covariate	No.	HR	95% Confidence interval	P
<b>OS</b>				
UCB HCT vs haploidentical HCT (mo)				
≤18		1.93	1.45-2.56	<.001
>18		0.68	0.38-1.21	.19
Remission status				
CR1	481	Reference		
CR2+	217	1.62	1.27-2.07	<.001
Karnofsky performance status (%)				
<90	259	Reference		
≥90	429	0.81	0.64-1.04	.10
Conditioning regimen				
MAC-TBI	380	Reference		
MAC-chemotherapy	74	2.14	1.45-3.14	<.001
RIC/NMA	243	1.22	0.93-1.59	.15
<b>LFS</b>				
UCB HCT vs haploidentical HCT (mo)				
≤18		1.40	1.09-1.79	.007
>18		0.58	0.31-1.07	.08
Remission status				
CR1	469	Reference		
CR2+	203	1.59	1.27-1.99	<.001
Race/ethnicity				
White Hispanic	144	Reference		
White non-Hispanic	310	0.86	0.65-1.13	.27
Black	83	1.33	0.93-1.89	.12
Asian	41	0.55	0.31-0.97	.04
Other/not specified	94	0.94	0.65-1.36	.74
Conditioning regimen				
MAC-TBI	364	Reference		
MAC-chemotherapy	72	1.77	1.23-2.55	.002
RIC/NMA	235	1.51	1.19-1.91	<.001
<b>NRM</b>				
Main effect				
Haploidentical HCT	381	Reference		
UCB HCT	291	2.08	1.45-2.99	<.001
Karnofsky performance status (%)				
<90	247	Reference		
≥90	416	0.65	0.46-0.90	.01
Conditioning regimen				
MAC-TBI	364	Reference		
MAC-chemotherapy	72	1.96	1.16-3.32	.01
RIC/NMA	235	0.88	0.59-1.29	.51
<b>Relapse</b>				
Main effect				
Haploidentical HCT	381	Reference		
UCB HCT	291	0.83	0.60-1.13	.23
Remission status				
CR1	469	Reference		

**Table 5. (continued)**

Covariate	No.	HR	95% Confidence interval	P
CR2+	203	1.88	1.40-2.53	<.001
Race/ethnicity				
White Hispanic	144	Reference		
White non-Hispanic	310	0.99	0.68-1.45	.98
Black	83	1.51	0.95-2.39	.08
Asian	41	0.55	0.26-1.19	.13
Other/not specified	94	0.73	0.43-1.25	.25
Conditioning regimen				
MAC-TBI	364	Reference		
MAC-chemotherapy	72	1.64	0.99-2.71	.05
RIC/NMA	235	2.01	1.47-2.74	<.001
<b>aGVHD, grade 2-4</b>				
Main effect				
Haploidentical HCT	376	Reference		
UCB HCT	285	1.83	1.46-2.30	<.001
<b>aGVHD, grade 3-4</b>				
Main effect				
Haploidentical HCT	376	Reference		
UCB HCT	285	1.97	1.35-2.88	<.001
<b>cGVHD</b>				
Main effect				
Haploidentical HCT	393	Reference		
UCB HCT	297	1.13	0.86-1.47	.38
Conditioning regimen				
MAC-TBI	375	Reference		
MAC-chemotherapy	71	1.11	0.72-1.72	.64
RIC/NMA	243	0.65	0.49-0.87	.003
HCT-CI				
0	169	Reference		
1	98	0.60	0.39-0.92	.02
2	105	0.91	0.63-1.31	.60
3+	317	0.68	0.50-0.91	.01

current recommendations<sup>26</sup> for using myeloablative TBI for conditioning in allo-HCT for adult ALL because of the reduced risk of relapse with similar or improved OS, but further study is warranted on optimal conditioning regimens across donor HCT types for adult ALL.

The primary reason for decreased NRM with haploidentical HCT compared with MUD HCT, 7/8 MMUD HCT, and UCB HCT seems to be significantly decreased rates of severe aGVHD and cGVHD with haploidentical HCT using PTCy. Death from GVHD was substantially higher in the non-haploidentical HCT cohorts and reduced quality of life from GVHD-related complications, although not assessed in this study, with other donor sources may be an additional reason to pursue haploidentical HCT with PTCy in the ALL population. On the basis of its success in haploidentical HCT, PTCy GVHD prophylaxis is being studied in MSD, MUD, and MMUD HCT. Existing studies evaluating alternative GVHD prophylaxis with PTCy for MSD and UD HCT<sup>27-30</sup> have consistently found low rates

of cGVHD, and these approaches may produce relative benefits similar to those seen with haploidentical HCT in this study for reducing GVHD and NRM. However, the impact of these approaches on relapse in the setting of fully HLA-matched donor HCT will need to be closely evaluated.

Although HRs for relapse favored non-haploidentical HCT modalities except HLA-identical sibling (HR, 0.81-0.83), this finding was not statistically significant and did not lead to inferior OS or LFS with haploidentical HCT using PTCy. When restricted to sites in the United States only, relapse was significantly higher with haploidentical HCT using PTCy compared with MUD HCT (HR, 0.76; 95% confidence interval, 0.61-0.96; *P* = .02), which raised some concern that relapse may be higher in some settings with haploidentical HCT, although in the same comparison, haploidentical HCT showed significantly better OS because of substantially lower NRM. A larger future study and longer follow-up are needed to evaluate whether the large and significant

**Table 6. Causes of death by cohort**

Characteristic	Haploidentical	MSD	MUD	7/8 HLA-MUD	UCB
No. of deaths	132	564	625	103	130
Cause of death					
ALL	64 (48)	293 (52)	240 (38)	33 (32)	40 (31)
Graft failure	1 (<1)	4 (<1)	1 (<1)	3 (3)	3 (2)
GVHD	7 (5)	81 (14)	126 (20)	25 (24)	16 (12)
Infection	28 (21)	98 (17)	126 (20)	21 (20)	30 (23)
Idiopathic pneumonia	4 (3)	5 (<1)	7 (1)	0	5 (4)
Acute respiratory distress syndrome	3 (2)	7 (1)	9 (1)	0	4 (3)
Organ failure	8 (6)	31 (5)	53 (8)	9 (9)	19 (15)
Organ toxicity	0	4 (<1)	1 (<1)	2 (2)	0
Secondary malignancy	2 (2)	4 (<1)	4 (<1)	2 (2)	2 (2)
Hemorrhage	3 (2)	4 (<1)	4 (<1)	1 (<1)	2 (2)
Accident or suicide	0	0	3 (<1)	0	0
Vascular	0	2 (<1)	1 (<1)	0	2 (2)
Other known	11 (8)	23 (4)	39 (6)	7 (7)	6 (5)
Unknown	1 (<1)	8 (1)	11 (2)	0	1 (<1)

reduction in aGVHD and cGVHD and death from GVHD with haploidentical HCT may be associated with a small increased risk of relapse after HCT. Non-severe aGVHD and cGVHD have previously been associated with reduced relapse,<sup>31</sup> and this study suggests that reducing GVHD with haploidentical HCT may have an impact on relapse. Consistent with this, MSD HCT and haploidentical HCT had similar rates of aGVHD and nearly identical risk of relapse (HR, 0.99).

A strength of this study is the large number of patients and international centers, which allows us to generalize the results, especially to centers in the United States. In addition, the large sample size in each cohort allowed adequate power to detect meaningful differences in outcomes between the HCT approaches. One limitation of this study is that it is retrospective. A prospective randomized study to better control for numerous variables would be needed to confirm our findings and address some limitations. For instance, the impact on outcomes from large centers favoring certain donor HCT modalities could influence the results. Another limitation is lack of standardized testing and definitions for MRD in data collected from sites. We found no differences in OS based on the CIBMTR definitions of MRD before HCT in contrast to a recent EBMT registry report.<sup>24</sup> However, well-defined MRD positivity before allo-HCT has been shown to predict poor outcomes with increased relapse and reduced survival after allo-HCT for ALL.<sup>32-40</sup> Reasons for our findings could be heterogeneity in testing, definitions of MRD used at different CIBMTR sites, and possibly a lack of sensitivity of MRD for predicting outcomes in a real-world setting. Another limitation of our study was an inability to evaluate the impact of central nervous system and extramedullary ALL on outcomes because the centers did not report these data. Follow-up for this study was also relatively short, given that haploidentical HCT has only come into widespread use in the last 5 years. Finally, our analysis was restricted to patients undergoing haploidentical HCT using PTCy, and our conclusions may not extend to alternate haploidentical HCT approaches. Approaches that use in vivo T-cell depletion or in vitro T-cell depletion and CD34<sup>+</sup> cell selection have shown promising outcomes in

ALL that seem to be comparable or possibly superior to MSD and MUD allo-HCT.<sup>41-48</sup> High-quality comparative studies are needed that compare well-matched populations undergoing T-cell replete haploidentical HCT using PTCy with approaches using in vivo T-cell depletion or in vitro T-cell depletion and CD34<sup>+</sup> cell selection.

Our findings support haploidentical HCT using PTCy as the preferred alternative donor HCT for ALL given the superior OS seen relative to 7/8 HLA-MUD and UCB HCT. Our data also suggest that OS is not different with haploidentical HCT using PTCy compared with traditional MSD and MUD HCT but with a reduced risk of GVHD. Although longer follow-up and confirmatory studies are needed, from this analysis haploidentical HCT seems to be an acceptable HCT option for all adult patients with ALL in remission that lacks anti-donor-specific HLA antibodies. To overcome the major causes of failure of haploidentical HCT uncovered in this study, future studies that aim to prevent relapse and reduce infectious death may further improve outcomes after haploidentical HCT. Future studies with longer follow-up will also be needed to definitively establish the role of haploidentical HCT using PTCy at different stages of ALL remission, particularly in the era of effective salvage treatments such as bispecific T-cell engagers, antibody-drug conjugates, and cellular therapies.

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## Authorship

Contribution: M.J.W. and L.M. conceived and designed the study; CIBMTR provided financial support and collected and assembled the data; M.J.W., L.M., M.d.L., W.S., M.-J.Z., and N.E.-M. analyzed the data; M.J.W., L.M., and M.d.L. prepared the first draft of the manuscript; and M.J.W., L.M., M.-J.Z., H.-L.W., N.E.-M., D.I.M., A.S.A.-H., L.M., N.C., D.R., R.P.G., S.M.G., M.C., A.M., S.G., V.R.B., S.S.P., F.V.M., Y.I., S.M.B., E.C., N.P., M.A.K.-D., H.M.L., S.G., C.B., M.A.D.P., R.C., B.N.S., K.B., R.M., B.W., U.B., M.A., A.B., H.S.M., J.A.Y., I.A., N.F., H.L., H.A.-A., E.K.W., M.S., M.D.S., M.v.d.P., M.R.G., J.L.L., R.T.K., J.M., R.M., J.-Y.C., J.W.L., C.O.F., M.M.K., L.E.W., U.G., S.N., R.F.O., L.F.V., A.S., O.R., B.D.F., J.C., H.C., S.C., T.N., S.S., B.G., L.A.B.-L., G.C.H., M.d.L., M.L., P.K., C.S.H., M.B.A., D.J.W., and W.S. interpreted the data, helped revise the manuscript, and gave final approval of the manuscript.

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