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blood advances

Transplant outcomes using older matched sibling donors compared with young alternative donors: a CIBMTR analysis

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Key Points

- Older, HLA-MSDs conferred similar survival to younger HLA-mismatched donors for HCT.
- Younger HLA-MUDs resulted in improved DFS compared with older HLA-MSD recipients.

Whether older HLA-matched sibling donors (MSD) are preferred over younger alternative donors for allogeneic hematopoietic cell transplantation (allo-HCT) with posttransplant cyclophosphamide (PTCy)-based graft-versus-host disease (GVHD) prophylaxis is unclear. We compared outcomes in allo-HCT recipients ≥50 years old after HCT from an older MSD (≥50 years) with recipients of younger (≤35 years) HLA-matched unrelated donor (MUD), haploidentical related donor (haplo), and HLA-mismatched unrelated donor (MMUD), grouped based on PTCy or calcineurin-inhibitor (CNI) based GVHD prophylaxis, that were reported to the Center for International Blood and Marrow Transplant Research between 2014 and 2021. The primary end point was overall survival (OS). Among 14 662 HCT recipients, 3746 received PTCy- and 10 916 CNI-based prophylaxis. In patients receiving PTCy-based HCT, the adjusted 5-year OS was similar between MSD and other donor types: 44% after MSD *versus* 52% after MUD (multivariable hazard ratio [HR]: 1.20; 95% confidence interval [CI], 1.03-1.41; $P = .09$), 45% after haplo donor (HR, 1.02; 95% CI, 0.88-1.18; $P = 1.00$), and 46% after MMUD (HR, 1.00; 95% CI, 0.83-1.21; $P = 1.00$). Compared with MSD, use of MUD associated with improved disease-free survival (DFS) with PTCy-based (HR, 1.21; 95% CI, 1.05-1.40; $P = .048$) and CNI-based (HR, 1.09; 95% CI, 1.04-1.15; $P < .01$) prophylaxis. Haplo donor use associated with worse OS compared with MUD use with PTCy (HR, 1.18; 95% CI, 1.05-1.33; $P = .04$). Older MSDs result in similar OS compared with

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

younger alternative donors; however, use of a younger MUD associated with improved DFS in older-aged recipients.

Introduction

Allogeneic hematopoietic cell transplantation (HCT) is an important consolidative therapy for patients with hematologic malignancy, and donor selection is a key component to this procedure.[1] Historically, a matched sibling donor (MSD) is typically prioritized over other graft sources such as HLA-matched unrelated donors (MUDs) or HLA-mismatched unrelated donors (MMUDs) because of improved outcomes, availability, and other considerations.[2] More recently, the use of posttransplant cyclophosphamide (PTCy)–based graft-versus-host disease (GVHD) prophylaxis demonstrates improved results after HLA-mismatched graft sources such as MMUDs and haploidentical (haplo)-related donors.[3,4] Improved GVHD outcomes are achieved with the use of PTCy after matched donor grafts such as MUD or MSD HCT.[5] A recent, large-scale registry-based analysis demonstrated similar survival between recipients of MUDs and single-loci MMUDs, suggesting that PTCy abrogates disparity in outcomes between HLA-matched and -mismatched donor sources.[3] Although effects of HLA mismatch may be mitigated with PTCy, younger donor age has remained a consistent prognostic predictor of patient survival both in the context of HLA-matched and -mismatched HCT with and without PTCy. Recent data suggest that the benefit of younger donor age supersedes HLA matching in the context of PTCy-based GVHD prophylaxis and that younger donors could be prioritized over HLA-matched donors.[6]

Here, we sought to evaluate whether donor age should be prioritized over other considerations, such as relatedness or HLA matching. We focused on HCT for older patients (aged ≥50 years), for whom the age differential sibling donors vs other graft sources is more likely and for whom the propensity for HCT-related toxicity is greater. We conducted a retrospective cohort analysis of patients who were reported to the Center for International Blood and Marrow Transplant Research (CIBMTR). The primary aim was to compare overall survival (OS) based on donor source in recipients undergoing HCT when PTCy was used. Secondary end points were other key clinical outcomes including disease-free survival (DFS) and nonrelapse mortality (NRM). We concurrently examined outcomes between older siblings and younger MUD after calcineurin inhibitor (CNI)–based GVHD prophylaxis as an internal control group. We hypothesized that younger alternative donors would result in improved outcomes compared with older MSDs when PTCy was used in older patients.

Methods

Data source

The CIBMTR is a research collaboration between the Medical College of Wisconsin and the National Marrow Donor Program that comprises a voluntary network of >500 transplantation centers worldwide that contribute baseline and posttransplantation data on consecutive HCTs to the CIBMTR research database.[7] The CIBMTR collects data at 2 levels, transplant essential data in all patients, and more comprehensive report forms in a subset of patients. Participating centers are required to report all transplantations consecutively and compliance is monitored by on-site audits. Computerized checks for discrepancies, physicians' review of submitted data, and on-site audits of participating centers ensure data quality. Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. The National Marrow Donor Program institutional review board approved this study. The study was performed in accordance with the Declaration of Helsinki.

Patient selection

HCT recipients aged ≥50 years with a diagnosis of acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), or myelodysplastic syndrome (MDS) and who underwent their first transplant between January 2014 and December 2021 using either an older-aged MSD (donor age: ≥50 years) or young (donor age: ≤35 years) 8/8 HLA-matched MUD, haplo donor, or MMUD (HLA match, ≤7/8) were included. The patient selection criteria are outlined in supplemental Table 1. Key exclusion criteria were HCT with ex vivo T-cell depletion, umbilical cord blood graft, and those receiving PTCy-based GVHD prophylaxis with antithymocyte globulin (ATG) and/or alemtuzumab. The study population was divided into 2 cohorts based on GVHD prophylaxis, and each with independent statistics.

Definitions and study end points

The primary end point was OS. Secondary end points were DFS, cumulative incidence of relapse, NRM, acute and chronic GVHD, and platelet/neutrophil engraftment. End points were determined from the time of transplantation; and standard criteria were used to define GVHD, relapse, and engraftment end points.[8-10]

Statistical analysis

Patient-, disease-, and transplant-related variables were compared using χ^2 statistics for categorical variables and the Kruskal-Wallis test for continuous variables. The probabilities of developing acute GVHD, chronic GVHD, NRM, and relapse were calculated using cumulative incidence method to accommodate competing risks. The Cox proportional hazards model was used in multivariate analyses for OS, DFS, NRM, relapse, and chronic GVHD, and logistic regression model was used for acute grade 2 to 4 GVHD and grade 3 to 4 acute GVHD. Variables considered in multivariate analysis include recipient age, sex, Karnofsky performance score, race/ethnicity, HCT-specific comorbidity index (HCT-CI), time from diagnosis to HCT, disease type, disease risk (European LeukemiaNet [ELN] 2017 for AML, revised International Prognostic Scoring System for MDS, and cytogenetic score for ALL), donor age, donor gender, graft type, HLA-DPB1 T-cell epitope (TCE) matching status, GVHD prophylaxis, conditioning regimen intensity, donor/recipient cytomegalovirus serostatus, year of HCT, and ATG/alemtuzumab use in the CNI cohort. Tests indicated that the proportionality assumptions hold. The final multivariate models

were built using a stepwise model selection approach. Each model contained the main effect for donor type groups because it is the main interest of this study. The potential interaction between main effect and all significant covariates were tested. No interactions were detected. The multivariable analysis grouped individuals with a missing or unspecified value as a missing category. Each adjusted variable had a small percentage of missing individuals: HCT-CI of <1%; donor/recipient cytomegalovirus serostatus of <1%; conditioning of <1%; Karnofsky performance status score of 2%; disease status of 4%; and race not reported of 6%. The stepdown Bonferroni method was applied to adjust for multiple comparisons in the PTCy cohort, and a P value $< .05$ was considered statistically significant. Finally, adjusted probabilities of OS and DFS, and adjusted cumulative incidence functions of NRM, relapse, acute GVHD, and chronic GVHD were calculated using the multivariate models, stratified on donor type of transplant, and weighted by the pooled sample proportion value for each prognostic factor. These adjusted probabilities estimate likelihood of outcomes in populations with similar prognostic factors. The center effect was tested using a random frailty model with gamma frailty distribution, which indicated that centers had a mild random effect for OS, DFS, and relapse.[11] However, there was no impact on any of the outcomes of donor types with center-effect adjustment.

Results

Baseline characteristics

Amongst 14 662 eligible patients, 3746 received PTCy-based GVHD prophylaxis from 173 centers. The baseline patient-, disease-, and transplant-related characteristics of the PTCy cohort are described in Table 1. The median follow-up of survivors was 36 months. Recipients' mean age at the time of HCT was 63 years, 61% were male, and 53% had an HCT-CI score of ≥3. Overall, 57% of patients had AML, 31% MDS, and 12% ALL. Regarding conditioning intensities, 38% underwent reduced intensity conditioning, 34% myeloablative *conditioning*, and 28% nonmyeloablative conditioning. The mean donor age of MSDs was 60 years (n = 540); MUDs, 26 years (n = 1221); haplo donors, 28 years (n = 1518); and MMUDs, 27 years (n = 467). The median time from diagnosis to HCT was 162 days, 186 days, 188 days, and 199 days in the MSD, MUD, haplo donor, and MMUD arms, respectively. Ninety-two percent of patients within the young MMUD group received HLA-7/8 matched donor grafts; and 6%, 1%, and 1% received HLA-6/8, 5/8, and 4/8 matched donor grafts, respectively. Within the young haplo donor group, 75% received HLA-4/8, 21% HLA-5/8%, and 4% HLA-6/8 matched donor grafts.

Among the 10 916 eligible patients from 231 centers that received CNI-based GVHD prophylaxis, 6010 underwent HCT using a young MUD and 4906 using an older-aged MSD. The baseline characteristics of the CNI cohort are provided in supplemental Table 2. The mean age of HCT recipients was 63 years and 56% of patients had AML, 34% MDS, and 10% ALL. Regarding conditioning intensities, 52% underwent reduced intensity conditioning, 42% myeloablative conditioning, and 6% nonmyeloablative conditioning. The mean donor age was 60 and 26 years, and the median time from diagnosis to HCT was 160 days and 182 days for older-aged MSDs vs young MUDs, respectively. The median follow-up of survivors in the CNI cohort was 48 months.

OS in the PTCy cohort

The adjusted 5-year OS was 44% (95% confidence interval [CI], 38-49) with older-aged MSDs vs 52% with young MUDs (95% CI, 48-56%; $P = .07$), 45% with haplo donors (95% CI, 41-48; $P = 1.00$), and 46% with MMUDs (95% CI, 39-52; $P = 1.00$; Table 2). In multivariable analysis, compared with older-aged MSDs, there was no significant difference in OS with haplo donors (hazard ratio [HR], 1.02; 95% CI, 0.88-1.18; $P = 1.00$) or MMUDs (HR, 1.00; 95% CI, 0.83-1.21; $P = 1.00$), and the higher OS observed with young MUDs did not reach statistical significance (HR, 1.20; 95% CI, 1.03-1.41; $P = .09$; Table 3; Figure 1A). Multivariable models did not demonstrate a difference in OS based on HLA-DPB1 TCE matching status (supplemental Table 3).

Within the young donor groups, young MUDs conferred a significantly higher OS than haplo donors (HR, 1.18; 95% CI, 1.05-1.33; $P = .04$), and the OS difference with MUDs vs MMUD did not reach statistical significance (HR, 1.20; 95% CI, 1.02-1.42; $P = .12$). No differences in OS were observed between the MMUD and haplo donor groups (HR, 1.02; 95% CI, 0.87-1.19; $P = 1.00$; supplemental Table 4).

Secondary outcomes in the PTCy cohort

The adjusted 5-year DFS was 38% (95% CI, 33-43) with older-aged MSDs vs 45% (95% CI, 42-49; $P = .07$) with young MUDs, 38% with haplo donors (95% CI, 35-41; $P = .92$), and 43% with MMUDs (95% CI, 37-48; $P = .75$; Table 2). In multivariable analysis, compared with older-aged MSD recipients, DFS was significantly better after young MUD donor HCT (HR, 1.21; 95% CI, 1.05-1.40; $P = .048$), and there was no difference compared with haplo donor (HR, 1.04; 95% CI, 0.90-1.19; $P = 1.00$) and MMUD HCT (HR, 1.07; 95% CI, 0.90-1.28; $P = 1.00$; Table 3; Figure 1B). Within the young donor groups, DFS was significantly higher after MUD HCT than haplo donor HCT (HR, 1.17; 95% CI, 1.05-1.31; $P = .038$). There was no significant difference in DFS with MMUD compared with either MUD (HR, 1.13; 95% CI, 0.97-1.33; $P = .47$) or haplo donor HCT (HR, 0.97; 95% CI, 0.83-1.13; $P = 1.00$) (supplemental Table 4).

Cumulative incidence of NRM at 5 years was 22% (95% CI, 17-28) for older-aged MSD vs 19% (95% CI, 15-22; $P = .55$), 30% (95% CI, 26-34; $P = .12$) and 23% (95% CI, 18-27; $P = .91$) for young MUD, haplo donor, and MMUD, respectively (Table 2). In multivariable analysis, corresponding HRs for NRM compared with older-aged MSD were 1.00 (95% CI, 0.77-1.30; $P = 1.0$) for MUD, 0.68 (95% CI, 0.53-0.88; $P = .01$) for haplo donor, and 0.74 (95% CI, 0.54-1.01; $P = .16$) for MMUD HCT (Table 3; Figure 1C). Within the young donor groups, NRM was significantly higher with haplo donor vs MUD HCT (HR, 1.47; 95% CI, 1.21-1.79; $P < .001$) and the difference in NRM between MMUD and MUD did not reach statistical significance (HR, 1.35; 95% CI, 1.04-1.76; $P = .09$) (supplemental Table 4).

Although the 5-year adjusted probabilities of relapse did not reach statistical significance, it was 48% (95% CI, 43-54) for older-aged MSD compared with 42% (95% CI, 37-46; $P = .33$), 41% (95% CI, 37-44; $P = .13$), and 41% (95% CI, 34-48; $P = .49$) for young MUDs, haplo donor, and MMUDs, respectively (Table 2). Corresponding HRs for relapse compared with older-aged MSDs was 1.29 (95% CI, 1.08-1.53; $P = .02$),1.30

Table 1. Baseline characteristics of older (age 50 years or above) patients who received PTCy-based GVHD prophylaxis

	Older MSD	Young MUD	Young haplo donor	Young MMUD	*P* value	Total
No. of patients	540	1221	1518	467		3746
Patient characteristics						
Patient age, y					<.01†	
Mean (SD)	62.1 (5.85)	64.7 (6.30)	60.9 (5.82)	62.7 (6.45)		62.5 (6.28)
Sex, n (%)					<.01*	
Male	311 (57.6)	769 (63.0)	994 (65.5)	222 (47.5)		2296 (61.3)
Female	229 (42.4)	452 (37.0)	524 (34.5)	245 (52.5)		1450 (38.7)
Karnofsky score, n (%)					.57*	
<90	262 (48.5)	583 (47.7)	730 (48.1)	230 (49.3)		1805 (48.2)
Race/ethnicity, n (%)					<.01*	
Asian	26 (4.8)	22 (1.8)	118 (7.8)	18 (3.9)		184 (4.9)
Black	40 (7.4)	18 (1.5)	207 (13.6)	50 (10.7)		315 (8.4)
White, non-Hispanic	382 (70.7)	1083 (88.7)	915 (60.3)	328 (70.2)		2708 (72.3)
White, Hispanic	38 (7.0)	37 (3.0)	170 (11.2)	44 (9.4)		289 (7.7)
Unknown/other‡	54 (10)	61 (5.0)	108 (7.1)	27 (5.8)		250 (6.7)
HCT-CI, n (%)					.20*	
≥3	281 (52.0)	670 (54.9)	774 (51.0)	263 (56.3)		1988 (53.1)
Donor characteristics						
Donor age, y					<.01†	
Mean (SD)	60.2 (5.65)	26.2 (4.14)	28.1 (4.50)	26.5 (4.02)		31.9 (12.5)
Donor sex, n (%)					<.01*	
Male	283 (52.4)	822 (67.3)	947 (62.4)	261 (55.9)		2313 (61.7)
Female	257 (47.6)	399 (32.7)	571 (37.6)	206 (44.1)		1433 (38.3)
Donor/recipient CMV serostatus n (%)					<.01*	
+/+	249 (46.1)	335 (27.4)	563 (37.1)	143 (30.6)		1290 (34.4)
+/–	56 (10.4)	117 (9.6)	81 (5.3)	72 (15.4)		326 (8.7)
–/+	118 (21.9)	416 (34.1)	475 (31.3)	143 (30.6)		1152 (30.8)
–/–	110 (20.4)	348 (28.5)	390 (25.7)	109 (23.3)		957 (25.5)
Not reported	7 (1.3)	5 (0.4)	9 (0.6)	0 (0.0)		21 (0.6)
Disease characteristics						
Primary disease, n (%)					<.01*	
AML	329 (60.9)	662 (54.2)	857 (56.5)	283 (60.6)		2131 (56.9)
ALL	50 (9.3)	119 (9.7)	211 (13.9)	61 (13.1)		441 (11.8)
MDS	161 (29.8)	440 (36.0)	450 (29.6)	123 (26.3)		1174 (31.3)
AML: ELN 2017 risk, n (%)					<.01*	
Normal	51 (15.5)	105 (15.9)	154 (18.0)	41 (14.5)		351 (16.5)
Favorable	26 (7.9)	86 (13.0)	118 (13.8)	20 (7.1)		250 (11.7)
Intermediate	111 (33.7)	164 (24.8)	227 (26.5)	73 (25.8)		575 (27.0)
Poor	128 (38.9)	296 (44.7)	341 (39.8)	143 (50.5)		908 (42.6)
APL	0 (0.0)	2 (0.3)	3 (0.4)	1 (0.4)		6 (0.3)
Not reported	13 (4.0)	9 (1.4)	14 (1.6)	5 (1.8)		41 (1.9)
ALL: cytogenetics, n (%)					.77*	
Normal	6 (12.0)	23 (19.3)	45 (21.3)	8 (13.1)		82 (18.6)
Poor	37 (74.0)	80 (67.2)	131 (62.1)	44 (72.1)		292 (66.2)

APL, acute promyelocytic leukemia; CMV, cytomegalovirus; IPSS-R, revised International Prognostic Scoring System; SD, standard deviation.
*Hypothesis testing: Pearson χ^2 test.
†Hypothesis testing: Kruskal-Wallis test.
‡Other race/ethnicity includes Native Hawaiian/Pacific Islander, American Indian/Alaska native, and multiple race.
§Other leukemia remission includes first or higher relapse, third or higher complete remission, and not reported.
||Other MDS remission status includes progression from hematologic improvement, relapse from complete remission, and not reported.

Table 1 (continued)

	Older MSD	Young MUD	Young haplo donor	Young MMUD	*P* value	Total
Other	4 (8.0)	12 (10.1)	23 (10.9)	6 (9.8)		45 (10.2)
Not reported	3 (6.0)	4 (3.4)	12 (5.7)	3 (4.9)		22 (5.0)
MDS: IPSS-R, n (%)					.55*	
Very low	3 (1.9)	8 (1.8)	5 (1.1)	1 (0.8)		17 (1.4)
Low	110 (68.3)	276 (62.7)	287 (63.8)	79 (64.2)		752 (64.1)
Intermediate	11 (6.8)	33 (7.5)	49 (10.9)	12 (9.8)		105 (8.9)
High	5 (3.1)	11 (2.5)	16 (3.6)	5 (4.1)		37 (3.2)
Very high	28 (17.4)	108 (24.5)	88 (19.6)	25 (20.3)		249 (21.2)
Not reported	4 (2.5)	4 (0.9)	5 (1.1)	1 (0.8)		14 (1.2)
Leukemia remission status, n (%)					<.01*	
First complete remission	268 (70.7)	613 (78.5)	787 (73.7)	260 (75.6)		1928 (75.0)
Second complete remission	52 (13.7)	79 (10.1)	152 (14.2)	45 (13.1)		328 (12.8)
Primary induction failure	37 (9.8)	61 (7.8)	98 (9.2)	24 (7.0)		220 (8.6)
Other§	22 (5.8)	28 (3.6)	31 (3)	15 (4.4)		96 (3.6)
MDS remission status, n (%)					.08*	
No response/stable disease	101 (62.7)	267 (60.7)	293 (65.1)	65 (52.8)		726 (61.8)
Hematologic improvement	25 (15.5)	80 (18.2)	69 (15.3)	23 (18.7)		197 (16.8)
Complete remission	25 (15.5)	73 (16.6)	64 (14.2)	26 (21.1)		188 (16.0)
Other‖	10 (6.2)	20 (4.5)	24 (5.4)	9 (7.3)		63 (5.4)
Transplant characteristics						
Graft type, n (%)					<.01*	
Bone marrow	57 (10.6)	115 (9.4)	322 (21.2)	79 (16.9)		573 (15.3)
Peripheral blood	483 (89.4)	1106 (90.6)	1196 (78.8)	388 (83.1)		3173 (84.7)
Time from diagnosis to transplant, d					<.01†	
Median (25-75 percentile)	162 (113-294)	186 (136-293)	188 (133-323)	199 (144-337)		186 (133-312)
GVHD prophylaxis, n (%)					<.01*	
PTCy + other(s)	499 (92.4)	1178 (96.5)	1516 (99.9)	464 (99.4)		3657 (97.6)
PTCy alone	41 (7.6)	43 (3.5)	2 (0.1)	3 (0.6)		89 (2.4)
Conditioning regimen intensity, n (%)					<.01*	
Myeloablative	242 (44.8)	438 (35.9)	457 (30.1)	136 (29.1)		1273 (34.0)
Reduced intensity	206 (38.1)	614 (50.3)	396 (26.1)	203 (43.5)		1419 (37.9)
Nonmyeloablative	92 (17.0)	168 (13.8)	665 (43.8)	127 (27.2)		1052 (28.1)
Unknown	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)		2 (<0.1)
Transplant years, n (%)					<.01*	
2014-2017	175 (32.4)	175 (14.3)	415 (27.3)	80 (17.1)		845 (22.6)
2018-2021	365 (67.6)	1046 (85.7)	1103 (72.7)	387 (82.9)		2901 (77.4)
Follow-up of survivors, median (range), mo	36 (3-101)	26 (3-100)	36 (3-104)	27 (3-89)		36 (3-104)

APL, acute promyelocytic leukemia; CMV, cytomegalovirus; IPSS-R, revised International Prognostic Scoring System; SD, standard deviation.
*Hypothesis testing: Pearson χ^2 test.
†Hypothesis testing: Kruskal-Wallis test.
‡Other race/ethnicity includes Native Hawaiian/Pacific Islander, American Indian/Alaska native, and multiple race.
§Other leukemia remission includes first or higher relapse, third or higher complete remission, and not reported.
‖Other MDS remission status includes progression from hematologic improvement, relapse from complete remission, and not reported.

(95% CI, 1.10-1.54; $P = .02$), and 1.26 (95% CI, 1.01-1.56; $P = .15$) for young MUD, haplo donor, and MMUD HCT, respectively (Table 3; Figure 1D). Within the young donor groups, there were no significant differences in the risk of relapse (supplemental Table 4).

Cumulative incidences of grade 2 to 4 acute GVHD at 6 months were 25% (95% CI, 22-28), 27% (95% CI, 25-29), 29% (95% CI, 26-31), and 26% (95% CI, 22-29) for MSD, MUD, haplo donor, and MMUD, respectively. Cumulative incidences of grade 3 to 4 acute GVHD at 6 months were 9% (95% CI, 7-12), 6% (95% CI,

Table 2. Five-year adjusted probabilities of end points by donor groups in the PTCy cohort

End points at 5 years	MSD, % (95% CI)	MUD, % (95% CI)	Haplo, % (95% CI)	MMUD, % (95% CI)
OS	44 (38-49)	52 (48-56)	45 (41-48)	46 (39-52)
DFS	38 (33-43)	45 (42-49)	38 (35-41)	43 (37-48)
NRM	22 (17-28)	19 (15-22)	30 (26-34)	23 (18-27)
Relapse	48 (43-54)	42 (37-46)	41 (37-44)	41 (34-48)
Acute grade 2-4 GVHD	25 (22-28)	27 (25-29)	29 (26-31)	26 (22-29)
Acute grade 3-4 GVHD	9 (7-12)	6 (5-8)	7 (6-9)	7 (4-9)
Chronic GVHD	23 (20-27)	22 (20-24)	25 (22-27)	26 (22-31)

5-8), 7% (95% CI, 6-9), and 7% (95% CI, 4-9) for MSD, MUD, haplo donor, and MMUD, respectively. Cumulative incidences of moderate to severe chronic GVHD at 12 months were 23% (95% CI, 20-27), 22% (95% CI, 20-24), 25% (95% CI, 22-27), and 26% (95% CI, 22-31), for MSD, MUD, haplo donor, and MMUD, respectively (Table 2). Multivariable analysis for grade 2 to 4, grade 3 to 4 acute, and moderate to severe chronic GVHD by donor groups are shown in Table 3 and supplemental Table 4. There were no significant differences in acute grade 2 to 4, acute grade 3 to 4 or chronic GVHD between the donor groups.

Univariable analysis for hematologic recovery is shown in supplemental Figures 1 and 2. Median time to neutrophil recovery was 16, 17, 18, and 17 days for MSD, MUD, haplo donor, and MMUD respectively ($P < .001$). Corresponding median time to platelet recovery were 21, 26, 28, and 26 days ($P < .001$), respectively. We found no significant interaction between time to HCT and the main effect in all multivariable models. There were also no interactions between disease risk (ELN2017 for AML; revised International Prognostic Scoring System for MDS; and cytogenetic score for ALL) or conditioning intensities and the main effect for all donor types.

CNI-based GVHD prophylaxis cohort

The 5-year adjusted probability of OS was 43% (95% CI, 42-45) compared with 44% (95% CI, 43-46; $P = .41$) for MSD and MUDs, respectively (Table 4; Figure 2A). In multivariable analysis, OS did not significantly differ between older-aged MSDs and younger MUDs (HR, 1.03; 95% CI, 0.97-1.09; $P = .37$; Table 5). Multivariable models did not demonstrate an association between HLA-DPB1 TCE matching status (supplemental Table 5).

Regarding secondary outcomes, the 5-year adjusted DFS by donor group is shown in Table 4 and Figure 2B, and 5-year adjusted NRM and relapse in supplemental Figures 3 and 4. In multivariate analysis, HCT with young MUDs showed superior DFS to older-aged MSDs (HR, 1.09; 95% CI, 1.04-1.15; $P < .01$; Table 5). There was no significant difference in NRM between the 2 donor groups (HR, 0.94; 95% CI, 0.86-1.03; $P = .16$). MSD had higher relapse than MUD (HR, 1.23; 95% CI, 1.15-1.33; $P < .0001$). Cumulative incidences of acute grade 2 to 4 (odds ratio, 0.77; 95% CI, 0.71-0.84; $P < .0001$) and moderate-to-severe chronic GVHD (HR, 0.86; 95% CI, 0.81-0.91; $P < .0001$) were significantly lower with MSD vs MUD. There was no significant difference in acute grade 3 to 4 GVHD (odds ratio, 0.99; 95% CI, 0.87-1.12; $P = .86$). Univariable analysis for hematologic recovery is shown in supplemental Figures 5 and 6. Median time to neutrophil recovery was 15 and 14 days in MSD and MUD, respectively. Median time to platelet recovery was 17 days in both donor groups.

Discussion

This retrospective registry analysis investigated whether use of young alternative donors leads to improved outcomes compared with older-aged MSDs for older HCT recipients. The primary findings of this study were that the use of younger alternative donors such as a related haplo donor, MUD, and MMUD resulted in similar OS to that with older MSDs and can be considered acceptable

Table 3. Multivariable analysis by donor group in the PTCy cohort

	MSD vs MUD			MSD vs haplo			MSD vs MMUD		
End points	HR/OR (95% CI)	P (Raw)	P* (Bonferroni)	HR/OR (95% CI)	P (Raw)	P* (Bonferroni)	HR/OR (95% CI)	P (Raw)	P* (Bonferroni)
OS†	1.20 (1.03-1.41)	.019	.096	1.02 (0.88-1.18)	.781	1	1.00 (0.83-1.21)	.979	1
DFS†	1.21 (1.05-1.40)	.01	.048	1.04 (0.90-1.19)	.61	1	1.07 (0.90-1.28)	.446	1
NRM†	1.00 (0.77-1.30)	.986	1	0.68 (0.53-0.88)	.003	.014	0.74 (0.54-1.01)	.055	.164
Relapse†	1.29 (1.08-1.53)	.004	.02	1.30 (1.10-1.54)	.003	.015	1.26 (1.01-1.56)	.038	.153
Grade 2-4 aGVHD‡	0.92 (0.73-1.16)	.49	1	0.88 (0.70-1.11)	.281	1	1.02 (0.76-1.35)	.917	1
Grade 3-4 aGVHD‡	1.55 (1.06-2.27)	.024	.141	1.30 (0.90-1.87)	.16	.638	1.46 (0.90-2.37)	.123	.615
Chronic GVHD†	1.09 (0.89-1.32)	.408	1	0.92 (0.76-1.11)	.375	1	0.85 (0.68-1.08)	.178	.712

aGVHD, acute GVHD; haplo, young, haploidentical donor; MMUD, young, mismatched unrelated donor; MSD, older-aged, matched sibling donor; MUD, young, matched unrelated donor; OR, odds ratio.

*Stepdown Bonferroni *P* value is reported to adjust for multiple comparisons in the PTCy cohort; 95% CI values are not adjusted for multiple comparisons.

†HR reported for OS, DFS, NRM, relapse, and chronic GVHD.

‡OR reported for grade 2 to 4, and grade 3 to 4 acute GVHD.

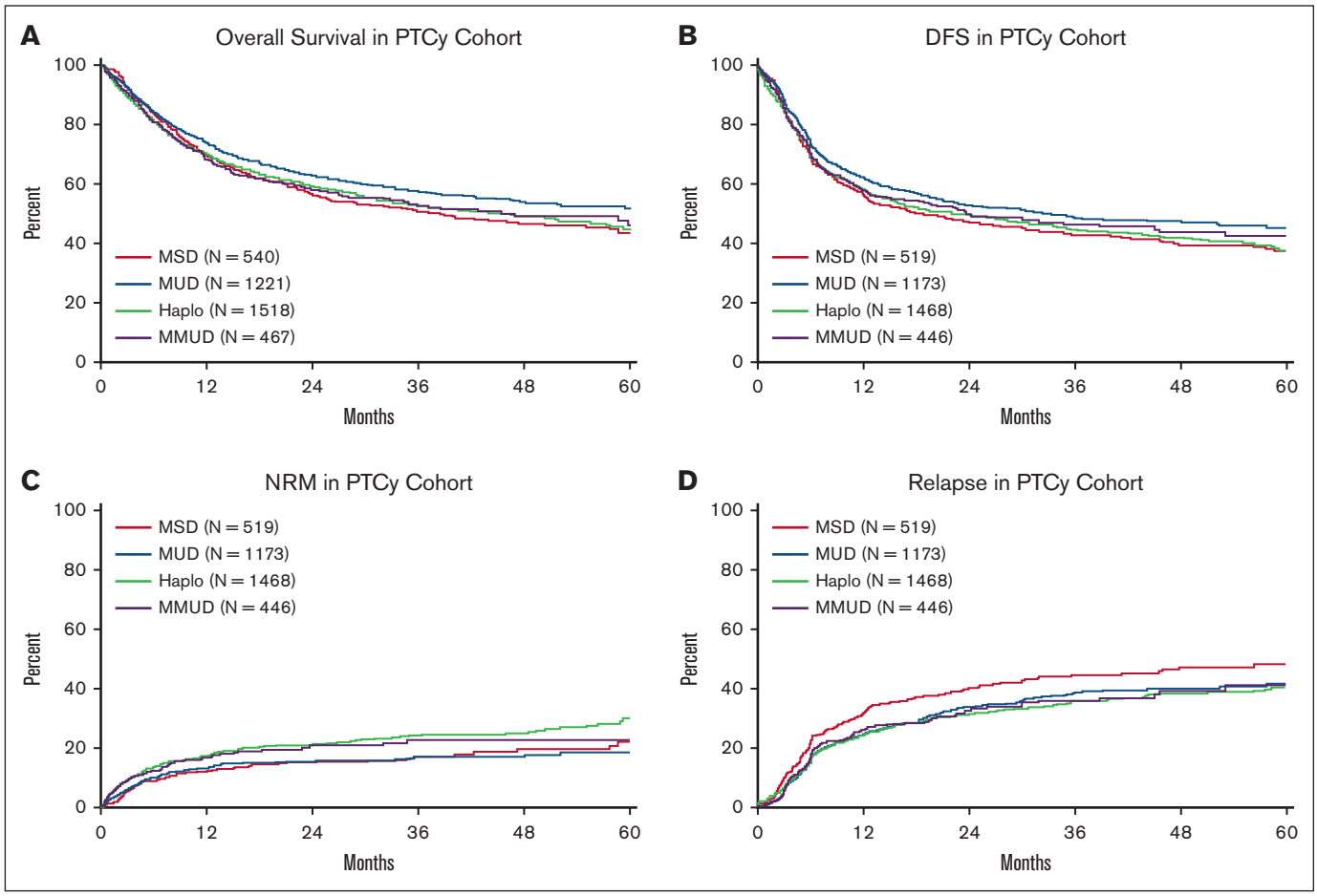

Figure 1. Adjusted outcomes in patients treated with PTCy. (A) OS by donor group. (B) DFS. (C) Cumulative incidences of NRM. (D) Cumulative incidences of relapse.

alternative donor sources when PTCy-based prophylaxis is used. DFS was superior with younger MUDs than older MSDs, suggesting that this may be the optimal donor source in older patients when available. However, given that DFS is a secondary study end point, this finding needs to be interpreted with caution. Nonetheless, the superior DFS with use of a young MUD was confirmed in recipients of HCT with CNI-based prophylaxis, suggesting that the benefit of donor age is not influenced by the GVHD prophylaxis program. A second finding was that young haplo donor HCT had inferior OS because of increased NRM compared with young MUD, suggesting that the latter may be preferred over a haplo donor when available. It should be noted that the NRM observed in haplo donor recipients in the present study was higher than that observed in previous clinical trial participants, or in another CIBMTR analysis, which may explain the decrement in outcomes observed in this group.[12,13] There were no other substantial differences in acute GVHD, chronic GVHD, hematopoietic recovery, or OS between the donor groups in the setting of PTCy-based GVHD prophylaxis.

Table 4. Adjusted probabilities of end points by donor groups in the CNI cohort

End points	MSD, % (95% CI)	MUD, % (95% CI)
OS at 5 years	43 (42-45)	44 (43-46)
DFS at 5 years	37 (36-39)	40 (38-41)
NRM at 5 years	29 (28-31)	32 (31-34)
Relapse at 5 years	43 (41-45)	37 (36-39)
Acute 2-4 GVHD at 6 months	30 (29-31)	35 (34-37)
Acute 3-4 GVHD at 6 months	12 (11-13)	12 (11-13)
Chronic GVHD at 12 months*	37 (36-39)	41 (39-42)

*Moderate-severe chronic GVHD.

Although there was no significant difference in the primary end point of OS, an important finding of this study is that use of an older MSD resulted in a significant decrement in DFS because of increased relapse compared with young MUDs across both the PTCy- and CNI-based GVHD prophylaxis programs. The biologic mechanism for improved disease control with young MUDs is not fully elucidated but may be explained by immune senescence and a higher immune-mediated graft-versus-leukemia effect with young donors.[14,15] Grafts from young MUDs have higher CD8 T-cell doses than their older-aged MSD counterparts and this may associate with improved disease control.[16] There is also a higher degree of recipient mismatches for minor histocompatibility antigens in MUDs and MMUDs than MSDs, which may have implications for our study findings.[17] Additionally, telomere attrition, clonal

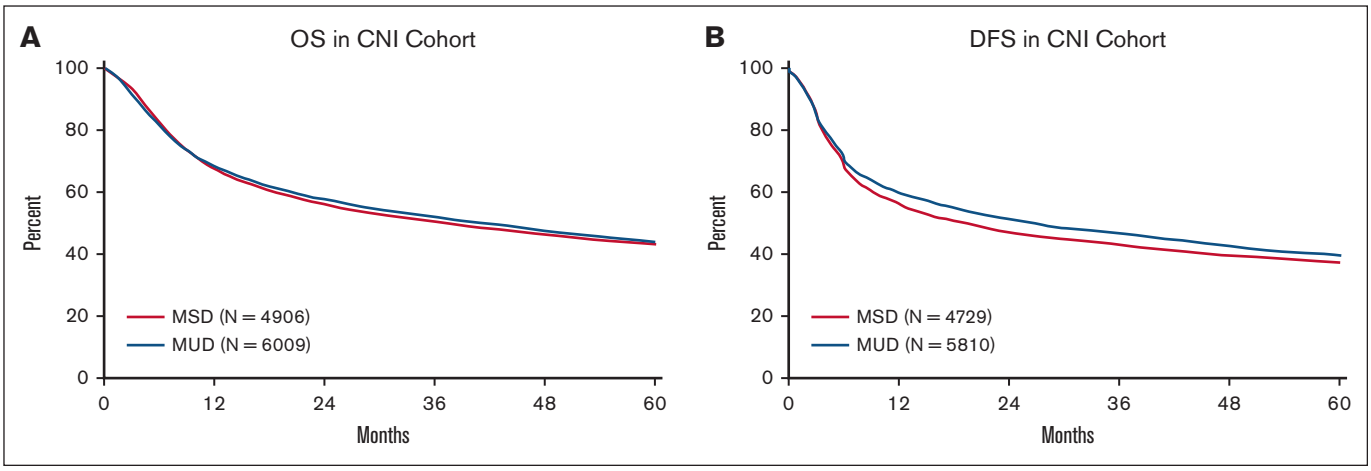

Figure 2. Adjusted outcomes in patients treated with CNI. (A) OS by donor group. (B) DFS. MSD, older-aged matched, sibling donor; MUD, young matched unrelated donor.

hematopoiesis of indeterminate potential mutations, and myeloid skewing occur with normal aging, but it is unclear whether these had any impact on our study findings.[18]

Barriers to HCT are being reduced by a broader variety of donor sources now available.[3,6] Given that the availability of a MUD varies by ancestry, the ability to perform safe and effective HCT with PTCy using haplo donors and MMUDs has eliminated donor availability barriers, particularly in ethnically diverse populations.[4,19] Of note, recent analyses from the European Society for Blood and Marrow Transplantation registry and the CIBMTR demonstrated that although younger donor age was associated with improved HCT outcomes, the presence of a single-allele mismatch did not influence outcomes in patients using PTCy.[3,6] In our study, we extend these findings in that we observed no difference in outcomes between older-aged MSD and younger MMUDs with PTCy. Within haplo donors, prior analyses have already shown that a young haplo donor should be preferred over older haplo donors.[6,20] Here, we found no significant differences in patient outcomes between use of a young MMUD and haplo donor, but our study findings cannot be used to inform selection between these 2 donor types and further analyses are required. As in prior CIBMTR reports, we observed improved outcomes with MUDs compared with haplo donors.[13] We observed no significant difference in OS based on HLA-DPB1 matching status within each of the donor groups. Indeed, findings from another CIBMTR study with a focus on HLA-DPB1 matching status has suggested that PTCy may abrogate detrimental effects of a nonpermissive mismatch at HLA-DPB1 in unrelated donor transplants and has the potential to further expand donor options.[21]

Table 5. Multivariable analysis by donor group in the CNI cohort

End point	MSD vs MUD HR (95% CI)	*P* value
OS	1.03 (0.97-1.09)	.3703
DFS	1.09 (1.04-1.15)	.0012
NRM	0.94 (0.86-1.03)	.1619
Relapse	1.23 (1.15-1.33)	<.0001
Chronic GVHD*	0.86 (0.81-0.91)	<.0001
End point	**MSD vs MUD OR (95% CI)**	***P* value**
Grade 2-4 acute GVHD	0.77 (0.71-0.84)	<.0001
Grade 3-4 acute GVHD	0.99 (0.87-1.12)	.8607

*Moderate-severe chronic GVHD.

In addition to donor availability, another potential advantage of using a related donor source compared with unrelated donors is the possibility of a shorter time to transplant.[22] Although we found that the median time from diagnosis to transplant was shorter with MSDs than unrelated donors, this difference was <1 month. Notably, the median time from diagnosis to HCT with a haplo-related donor was comparable with that with unrelated donor sources, and it is possible that haplo donors were only considered after searching for MUDs. We tested for and found no significant interaction between time to HCT and the main effect in all multivariable models. Similarly, we found no interactions between disease risks or conditioning intensities and the main effect for donor types.

Within recipients of CNI-based GVHD prophylaxis, our results confirmed findings from recent smaller, disease-specific CIBMTR analyses that using young MUDs offers improved disease control compared with older MSDs.[23-25] We also observed a higher risk for acute grade 2 to 4 and chronic GVHD with young MUDs. However, unlike the prior studies, we observed no increase in NRM in the young MUD group and this may relate to the prior studies being performed at earlier time periods (2011-2018) than our analysis. Notably, our findings also differ from those of a prior landmark CIBMTR study by Alousi et al of ~2000 older-aged HCT recipients from 1995 to 2005.[25] That study found that in patients with a high performance score, OS was lower with younger MUDs than older MSDs, whereas no differences were observed in recipients with a performance score of <90. However, young MUDs were defined as those aged <50 years in the prior analysis. We chose to use an age of ≤35 years as the cutoff for young donors based on registry outcomes demonstrating a survival advantage with these donors.[26] There have also been major advances in supportive care between the study periods from 1995 to 2005 from the prior study, to 2014 to 2021.

The retrospective nature of the study limits additional information regarding clinician decisions on donor choice. Additionally, there is the potential for residual confounding because of differences in patient baseline characteristics between donor groups. Although the stepdown Bonferroni method was used to adjust for multiple comparisons, this may be seen as a study limitation. Future prospective trials will be required to formally address any unforeseen selection bias. In its absence, and despite including a variety of disease types, this large registry analysis provides a valuable, high-quality data set. There was also no impact on any of the outcomes of donor types with center-effect adjustment. A combined analysis across GVHD prophylactic regimens was considered but limited by the more varied donor types used with PTCy. The disparate HR, for OS amongst MSD vs MUD with PTCy (HR, 1.20) and CNI-based prophylaxis (HR, 1.03) also indicate that there is likely an effect from the GVHD prophylactic regimen, warranting a separate analysis as performed here. We acknowledge that some centers may use ATG or alemtuzumab with PTCy. However, we excluded the use of PTCy with ATG/alemtuzumab to allow for greater homogeneity of the study population, and, furthermore, the use of PTCy with ATG/alemtuzumab was very limited in our original cohort (3.8% of PTCy cohort). Details regarding patient socioeconomic status, donor characteristics such as clonal hematopoiesis of indeterminate potential mutations, graft T-cell compositions, and AML risk stratification by ELN 2022 were not available for analysis. Because of limited data in earlier years of the study period regarding the time of onset of acute GVHD and administration of systemic therapy in those with chronic GVHD, GVHD-free relapse-free survival could not be evaluated as a composite end point. Finally, we did not include patients who received GVHD prophylaxis using abatacept, which is a more recently approved GVHD prophylaxis strategy.[27]

In conclusion, our study demonstrates that in patients aged ≥50 years with acute leukemia or MDS, HCT with older-aged MSDs results in OS similar to that with young alternative donors. MUDs aged ≤35 years associates with an improvement in DFS because of a lower incidence of relapse than with MSDs aged ≥50 years with either PTCy- or CNI-based GVHD prophylaxis, and improved OS compared with haplo donors aged ≤35 years when PTCy is used.

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Authorship

Contribution: K.N., B.C.S., and H.C. designed the initial study protocol; S.R.S. provided support for the overall study design and implementation; M.-J.Z. and M.B. performed the statistical analysis; K.N. drafted the manuscript; and all authors reviewed and participated in the revisions of the manuscript.

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