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Haploidentical

Who Is a Better Donor for Recipients of Allogeneic Hematopoietic Cell Transplantation: A Young HLA-Mismatched Haploidentical Relative or an Older Fully HLA-Matched Sibling or Unrelated Donor?

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A B S T R A C T

T cell replete HLA-mismatched haploidentical transplantation (HIDT) with post-transplant cyclophosphamide is increasingly becoming an acceptable treatment approach for patients lacking timely access to a suitably matched related donor transplant (MRDT) or matched unrelated donor transplant (MUDT). Multiple recent registry and single-center studies have shown comparable overall survival (OS) and disease-free survival (DFS) rates among HIDT, MRDT, and MUDT with a significantly lower risk of acute and chronic graft-versus-host disease (GVHD) among HIDT recipients. Candidates for allogeneic hematopoietic stem cell transplantation (HSCT) often have access to multiple donor sources, and a relevant question is whether outcomes can be improved with a younger HLA-mismatched haploidentical donor (≤35 years) rather than an older matched related donor (≥35 years) or matched unrelated donor (≥35 years). We analyzed 406 consecutive allogenic HSCT recipients, with a median age of 54 years (range, 19 to 77), after a MRDT with a donor age of ≥35 years (n = 222), MUDT with a donor age of ≥35 years (n = 91), and HIDT with a donor age of ≤35 years (n = 93). Median follow-up time for survivors was 51.5 months. Compared with MRDT and MUDT, HIDT recipients had a similar median age at time of HSCT, hematopoietic cell transplant comorbidity index, disease risk index distribution, and donor recipient sex matching. The survival estimates and relapse incidence at 3 years post-HSCT were OS (64% for MRDT, 54% for MUDT, and 62% for HIDT), DFS (55% for MRDT, 44% for MUDT, and 58% for HIDT), Transplant related mortality (TRM) (19% for MRDT, 16% for MUDT, and 18% for HIDT), and relapse (26% for MRDT, 37% for MUDT, and 24% for HIDT). HIDT recipients had better 3-year relapse rates compared with MUDT recipients (24% versus 37%, *P* = .048), with similar DFS and OS in a univariate analysis. MRDT recipients had a better relapse rate (26% versus 37%, *P* = .042) compared with MUDT recipients. Recipients of HIDT also had significantly lower rates of moderate to severe chronic GVHD compared with MRDT and MUDT recipients (*P* = .01). Multivariable analysis showed no effect of donor on OS, DFS, relapse, and TRM. Recipients of HIDT from a young donor ≤35 years had similar OS, lower rates of chronic GVHD, and better chronic GVHD-free, relapse-free survival compared with patients undergoing transplantation with an MRD or a MUD donor ≥35 years. This study suggests that given a situation where a choice between a young haploidentical relative and an older matched unrelated donor is to be made, one can achieve similar survival with a haploidentical donor and significantly lower rates of chronic GVHD.

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is a potentially curative therapy for patients with life-threatening hematologic malignancies [1]. More than 20,000 HSCTs are performed each year in the United States [2]. This number is predicted to continue to rise with improved supportive care measures, reduced-intensity conditioning regimens (RICs), and increased donor availability with the use of alternative graft sources [2]. Alternative and acceptable donor options for patients lacking a suitably matched sibling or unrelated donor include cord blood grafts or a HLA-mismatched haploidentical relative.

Although there have been exciting advances in HSCT, patients may experience certain barriers to transplantation, such as finding a suitable HLA-matched related donor (MRD) or an HLA-matched unrelated donor (MUD). This is particularly

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a concern for patients who do not have an MRD and are in urgent need of transplantation [3]. Furthermore, ethnic minorities such as African Americans, Hispanics, Asians, Pacific Islanders, and Native Americans continue to be underrepresented in donor volunteer registries [4,5].

T cell replete HLA-haploidentical donor transplantation (HIDT) with post-transplant cyclophosphamide is increasingly considered an acceptable alternative for patients lacking timely access to an optimal matched related donor transplant (MRDT) or matched unrelated donor transplant (MUDT) [6-8]. Multiple registry and single-center studies demonstrated comparable overall survival (OS) and disease-free survival (DFS) rates among MUD, MRD, and haploidentical donor sources [6,8-10]. These comparable outcomes with the use of alternative graft sources has increased the availability of potential donors. This creates a challenge in the selection of an optimal donor for allogeneic HSCT as patients may have access to multiple donor sources, and selecting the most appropriate donor remains an area of ongoing study. Previous evidence has suggested an association with age, sex, parity, race/ethnicity, cytomegalovirus serostatus, and ABO blood type on transplant outcomes [11-15]. This study focused on advanced donor age as it has been found to correlate with an increased incidence of graft-versus-host disease (GVHD) and a decrease in progression-free survival [11,12,16]. The purpose of our study is to examine the outcomes of using a young haploidentical donor rather than an older MRD or MUD in allogeneic HSCT recipients.

METHODS

Objective and Definition

The objective of this single-institution retrospective analysis is to assess whether a young HLA-mismatched haploidentical relative donor yields better transplant-related outcomes than an older MRD or MUD donor. An age cutoff of 35 years was chosen where haploidentical donors <35 years and recipients of MRD or MUD transplantations from donors >35 were included in the analysis. The age cutoff of 35 years was chosen based on median age of unrelated donors in prior National Marrow Donor Program reports [12].

Endpoints

Outcomes analyzed were OS (time from transplantation to death), DFS (survival without evidence of relapse of the underlying malignancy after transplantation), and nonrelapse mortality (NRM), relapse/progression of malignancy, acute GVHD, and chronic GVHD (cGVHD). The maximum cumulative incidence of acute GVHD was assessed 6 months after transplantation because of the possibility of delayed onset of clinical acute GVHD with transplantations performed using RIC/nonablative conditioning regimens. cGVHD was classified as mild, moderate, or severe by 2005 National Institutes of Health consensus criteria [17]. Acute GVHD and cGVHD were prospectively evaluated, graded, and documented by a single practitioner within the program. GVHD-free, relapse-free survival (GRFS) as a composite endpoint was defined by being free of the following parameters: grade 3 to 4 acute GVHD, relapse, cGVHD requiring immunosuppression, and death. cGVHD-free, relapse-free survival (cGRFS) was defined as survival free of relapse and cGVHD.

Demographics and Clinical Factors

Patient-, disease-, and transplant-related variables were prospectively documented and obtained for this analysis from our comprehensive institutional database. Demographics and clinical factors examined included age, sex, race, year of transplant (2005 to 2010, 2011 to 2013, 2014 to 2016), diagnosis, conditioning intensity (RIC/nonablative, myeloablative conditioning (MAC)), donor type (MRD, MUD, haploidentical donor), graft source (bone marrow, peripheral blood stem cells), HSCT comorbidity index [18], donor/recipient sex match, donor/recipient cytomegalovirus status, Center for International Blood and marrow Transplant Research (CIBMTR) risk score, disease risk index (DRI), GVHD prophylaxis tacrolimus, and methotrexate.

Statistical Analysis

Kaplan-Meier method was used to estimate the survival probabilities. The cumulative incidences of NRM, relapse, and acute GVHD and cGVHD were computed to accommodate for competing risks. NRM and relapse were considered competing risks. Death was considered the competing risk for GVHD endpoints. Log-rank test and Gray's test were used to compare survival probabilities and cumulative incidence probabilities over the entire time period, respectively. Comparison at a selected time point post-HSCT was performed by using the Wald test. In multivariable analysis, donor was retained in the Cox models for OS, DFS, relapse, and NRM. Other variables were selected if their *P*values were <.05. The proportional hazards assumption was tested by creating and including the time-dependent variable for a covariate. All the models passed the proportionality tests. Statistical analyses were performed by using the SAS software (version 9.4; SAS Institute, Cary, NC).

Study Population

In total, 406 patients who underwent a first allogeneic HSCT at our center between 2005 and 2016 met the selection criteria and were included in this analysis. The patients excluded from the analysis included 32 HIDTs with a donor age ≥35 years, 37 MRDTs with a donor age ≤35 years, and 201 MUDTs with a donor age ≤35 years. Patients underwent transplantation using an HLA-identical sibling donor age >35 years (MRD, n = 222); 8 of 8 HLA-A, HLA-B, HLA-C, and DRB1 allele volunteer matched unrelated donor age >35 years (MUD, n = 91); or T-replete haploidentical donor age <35 years (Haplo, n = 95). The transplants were performed consecutively between January 2006 and December 2016. This time frame was chosen to allow a minimum of 12 months of post-transplant follow-up for surviving patients. Haploidentical donors were selected based on our center criteria that make patients eligible for haploidentical donors if there is no suitable MRD or MUD donor or such a donor is not available within an acceptable time frame. Transplants using cord blood or grafts that were ex vivo T cell depleted were excluded from the analysis. GVHD prophylaxis for all haploidentical recipients entailed tacrolimus, mycophenolate, and post-transplant cyclophosphamide.

RESULTS

Patient and Donor Characteristics

Table 1 displays patient and donor characteristics. In total, 406 consecutive patients who underwent first allogeneic HSCT for hematologic malignancy at our center between 2005 and 2016 were included in this analysis. Median follow-up for survivors was 51.5 months (range, 5.2 to 143.6 months). The median donor age for HIDT was 27 years (range, 15 to 34 years) and was significantly younger ($P < .001$) than that for MRDT (53 years; range, 35 to 77 years) and MUDT (41 years; range, 35 to 54 years). Compared with MRDT and MUDT recipients, HIDT recipients had a similar HSCT comorbidity index, DRI distribution, and donor recipient sex matching. Recipients of HIDT were younger than recipients of MRDT and MUDT ($P = .045$). Recipients of HIDT were more likely to have received total body irradiation (TBI)-based myeloablative conditioning (39% versus 18% and 11% for MUDT and MRDT, $P < .001$), more likely to have received a bone marrow graft source (33% versus 11% and 2% for MUDT and MRDT, $P < .001$), and more likely to be transplanted after 2011 (79% versus 56% and 56% for MUDT and MRDT, $P < .001$).

OS, DFS, and Relapse

The survival estimates at 1 and 3 years, respectively, post-HSCT were as follows: OS, 80% and 64% for MRDT, 79% and 54% for MUDT, and 79% and 62% for HIDT; DFS, 69% and 55% for MRDT, 61% and 44% for MUDT, and 66% and 58% for HIDT; and transplant related mortality (TRM), 11% and 19% for MRDT, 8% and 16% for MUDT, and 12% and 18% for HIDT (Table 2).

In a time point analysis at 3 years after allogeneic HSCT, HIDT recipients had better 3-year relapse rates (24% versus 37%, $P = .048$) compared with MUDT recipients with similar OS and DFS (Table 2). MRDT recipients also had better relapse (26% versus 37%, $P = .042$) compared with MUDT recipients. When limiting the analysis to recipients age ≥50 years (n = 258), there was no difference in OS, DFS, or relapse between the 3 donor sources (Figure 1).

Table 1
Cohort Characteristics (N = 406)

Characteristic	Whole Cohort	MRD ≥35 yr	MUD ≥35 yr	Haploidentical <35 yr	*P* Value
No.	406	222	91	93	
Patient age, median (minimum, maximum), yr	54 (19, 77)	54 (29, 77)	54 (19, 73)	53 (20, 70)	
Patient age, n (%)					.045
19-49	148 (36)	69 (31)	36 (40)	43 (46)	
50-59	141 (35)	85 (38)	25 (27)	31 (33)	
60+	117 (29)	68 (31)	30 (33)	19 (20)	
Male sex, n (%)	237 (58)	128 (58)	51 (56)	58 (62)	.651
Race, n (%)					<.001
White	308 (76)	177 (80)	82 (90)	49 (53)	
Black	80 (20)	34 (15)	7 (8)	39 (42)	
Other/unknown	18 (4)	11 (5)	2 (2)	5 (5)	
Diagnosis, n (%)					.771
AML	150 (37)	86 (39)	33 (36)	31 (33)	
ALL	48 (12)	21 (9)	11 (12)	16 (17)	
MDS/MPS/CML	92 (23)	50 (23)	23 (25)	19 (20)	
NHL/HD/CLL	93 (23)	52 (23)	20 (22)	21 (23)	
MM	16 (4)	10 (4)	2 (2)	4 (4)	
AL	4 (1)	1 (1)	1 (1)	2 (2)	
PCD	3 (1)	2 (1)	1 (1)	0 (0)	
Conditioning intensity, n (%)					<.001
Reduced intensity	205 (50)	107 (48)	48 (53)	50 (54)	
Myelo TBI	76 (19)	24 (11)	16 (18)	36 (39)	
Myelo non-TBI	125 (31)	91 (41)	27 (30)	7 (7)	
Cell source, n (%)					<.001
Bone marrow	45 (11)	4 (2)	10 (11)	31 (33)	
Peripheral blood	361 (89)	218 (98)	81 (89)	62 (67)	
HSCT-CI, n (%)					.613
0-2	227 (56)	121 (55)	55 (60)	51 (55)	
≥3	179 (44)	101 (45)	36 (40)	42 (45)	
CIBMTR risk, n (%)					.423
Low	153 (52)	86 (39)	31 (34)	36 (39)	
Intermediate	92 (25)	46 (21)	20 (22)	26 (28)	
High	142 (19)	83 (37)	33 (36)	26 (28)	
NA or unknown	19 (4)	7 (3)	7 (8)	5 (5)	
DRI, n (%)					.712
Low	49 (12)	21 (9)	15 (16)	13 (14)	
Intermediate	213 (52)	122 (55)	45 (49)	46 (49)	
High	111 (27)	61 (28)	23 (25)	27 (29)	
Very high	23 (6)	13 (6)	6 (7)	4 (4)	
NA or unknown	10 (3)	5 (2)	2 (2)	3 (3)	
Donor age, median (minimum, maximum), yr	45 (15, 77)	53 (35, 77)	41 (35, 54)	27 (15, 34)	.001
Donor age, n (%)					<.001
15-24	37 (9)	—	—	37 (40)	
25-34	56 (14)	—	—	56 (60)	
35-44	108 (26)	48 (22)	69 (76)	—	
45-54	100 (25)	78 (35)	22 (24)	—	
55-64	64 (16)	59 (27)	0 (0)	—	
≥65	41 (10)	37 (17)	0(0)	—	
Donor/recipient sex, n (%)					.567
Female/female	75 (18)	46 (21)	16 (18)	13 (14)	
Male/male	147 (36)	75 (24)	36 (40)	36 (39)	
Female/male	90 (22)	53 (24)	15 (16)	22 (24)	
Male/female	94 (23)	48 (22)	24 (26)	22 (24)	
Donor/recipient CMV, n (%)					<.001
+/+	173 (43)	100 (45)	22 (24)	51 (55)	
−/−	83 (20)	42 (19)	29 (32)	12 (13)	
+/−	48 (12)	27 (12)	17 (19)	4 (4)	

(*continued*)

Table 1 (*Continued*)

Characteristic	Whole Cohort	MRD ≥35 yr	MUD ≥35 yr	Haploidentical <35 yr	*P* Value
−/+	101 (25)	52 (24)	23 (25)	26 (28)	
GVHD prophylaxis: tacrolimus, n (%)	368 (91)	191 (86)	85 (93)	92 (99)	.006
GVHD prophylaxis: methotrexate, n (%)	260 (64)	175 (79)	84 (92)	1 (1)	<.001
GVHD prophylaxis: post-transplant cyclophosphamide, n (%)	93 (23)	0 (0)	0 (0)	93 (100)	<.001
Year of transplant, n (%)					<.001
2005-2010	157 (39)	97 (44)	40 (44)	20 (22)	
2011-2013	111 (27)	60 (27)	14 (15)	37 (40)	
2014-2016	138 (34)	65 (29)	37 (41)	36 (39)	

AML indicates acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndrome; MPS, myeloproliferative syndrome; CML, chronic myelogenous leukemia; NHL, non-Hodgkin lymphoma; HD, Hodgkin's disease; CLL, chronic lymphocytic leukemia; MM, multiple myeloma; AL, acute leukemia; PCD, plasma cell disorder; TBI, total body irradiation; HSCT-CI, HSCT comorbidity index; CIBMTR, Center for International bone marrow transplant Research; NA, not applicable; CMV, cytomegalovirus.

Table 2
Survival, Incidence Estimates, and 3-Year Time Point Comparison

Outcome	Donor Source	1 yr	3 yr		
		Estimate (95% CI)	Estimate (95% CI)	Comparison at 3-yr Time Points	*P*Value*
OS	MRD ≥35	80 (74-85)	64 (57-70)	MRD versus MUD	.1386
	MUD ≥35	79 (69-86)	54 (42-64)	MRD versus Haplo	.7396
	Haplo <35	79 (69-86)	62 (50-71)	MUD versus Haplo	.3315
DFS	MRD ≥35	69 (62-74)	55 (48-62)	MRD versus MUD	.1019
	MUD ≥35	61 (50-70)	44 (33-55)	MRD versus Haplo	.6002
	Haplo <35	66 (55-74)	58 (47-68)	MUD versus Haplo	.0695
Relapse	MRD ≥35	20 (16-25)	26 (20-31)	MRD versus MUD	.0421
	MUD ≥35	31 (23-39)	37 (28-45)	MRD versus Haplo	.7251
	Haplo <35	22 (14-31)	24 (15-33)	MUD versus Haplo	.0484
TRM	MRD ≥35	11 (8-16)	19 (14-25)		
	MUD ≥35	8 (3-15)	16 (9-25)		
	Haplo <35	12 (7-20)	18 (11-27)		
All-grade cGVHD	MRD ≥35	47 (42-52)	51 (45-57)		
	MUD ≥35	48 (38-57)	53 (43-62)		
	Haplo <35	38 (28-47)	40 (31-49)		
Moderate to severe cGVHD	MRD ≥35	36 (30-41)	38 (33-44)		
	MUD ≥35	35 (26-45)	45 (35-55)		
	Haplo <35	23 (15-32)	23 (15-32)		

TRM indicates Transplant related mortality.
* Wald test was performed and *P* values are provided in the table.

GVHD and Composite Endpoints

The incidences of grade 2 to 4 acute GVHD and grade 3 to 4 acute GVHD at 180 days was 24% (95% confidence interval [CI], 20% to 28%) and 7% (95% CI, 4% to 10%) for MRDT, 56% (95% CI, 48% to 64%) and 19% (95% CI, 13% to 26%) for MUDT, and 39% (95% CI, 31% to 47%) and 10% (95% CI, 5% to 17%) for HIDT (Table 3). Recipients of HIDT had a significantly lower cumulative incidence of grade 2 to 4 acute GVHD compared with MUDT recipients ($P = .009$) (Figure 2A).

The incidence of moderate to severe cGVHD at 1 and 3 years, respectively, was 23% (95% CI, 15% to 23%) and 23% (95% CI, 15% to 23%) for HIDT compared with 36% (95% CI, 30% to 41%) and 38% (95% CI, 33% to 44%) for MRDT and 35% (95% CI, 26% to 45%) and 45% (95% CI, 35% to 55%) for MUDT recipients (Table 2). Recipients of HIDT had a significantly lower cumulative incidence of moderate to severe cGVHD compared with MUDT ($P = .010$) and MRDT ($P = .014$) recipients (Figure 2B).

The GRFS estimates at 3 years were 37% for HIDT, 24% for MUDT, and 29% for MRDT. On a pointwise comparison at 3 years, recipients of HIDT had better GRFS than MUDT recipients ($P = .01$) and a similar GRFS to MRDT recipients ($P = .10$). The estimates for cGRFS at 3 years were significantly better after HIDT at 43% compared with MUDT 24% ($P = .004$) and MRDT 30% ($P = .01$).

Multivariable Analysis

In multivariable analysis to assess the impact of donor on OS, DFS, relapse, and NRM, the choice of donor did not affect any of these endpoints (Table 4). For OS, recipient age (≥55 years versus <55 years; hazard ratio [HR], 1.49; 95% CI, 1.08 to 2.06; $P = .017$), race (black versus white; HR, 0.60; 95% CI, 0.37 to 0.98; $P = .043$), disease risk DRI (high/very high versus low/intermediate; HR, 1.90; 95% CI, 1.39 to 2.60; $P < .0001$), and HSCT comorbidity index (≥3 versus 0 to 2; HR, 1.67; 95% CI, 1.21 to 2.30; $P = .002$) were all associated with OS. DRI (high/very high versus low intermediate; HR, 2.22; 95% CI, 1.67 to 2.96; $P < .001$) and recipient age (≥55 years versus <55 years; HR, 1.46; 95% CI, 1.09 to 1.95; $P = .01$) were significant for lower DFS. For relapse risk, DRI (high/very high versus low intermediate; HR, 3.18; 95% CI, 2.16 to 4.67; $P < .001$) and year of transplant (2014 to 2016 versus 2005 to 2010; HR, 0.50; 95% CI, 0.3 to 0.83; $P = .008$) were significant factors.

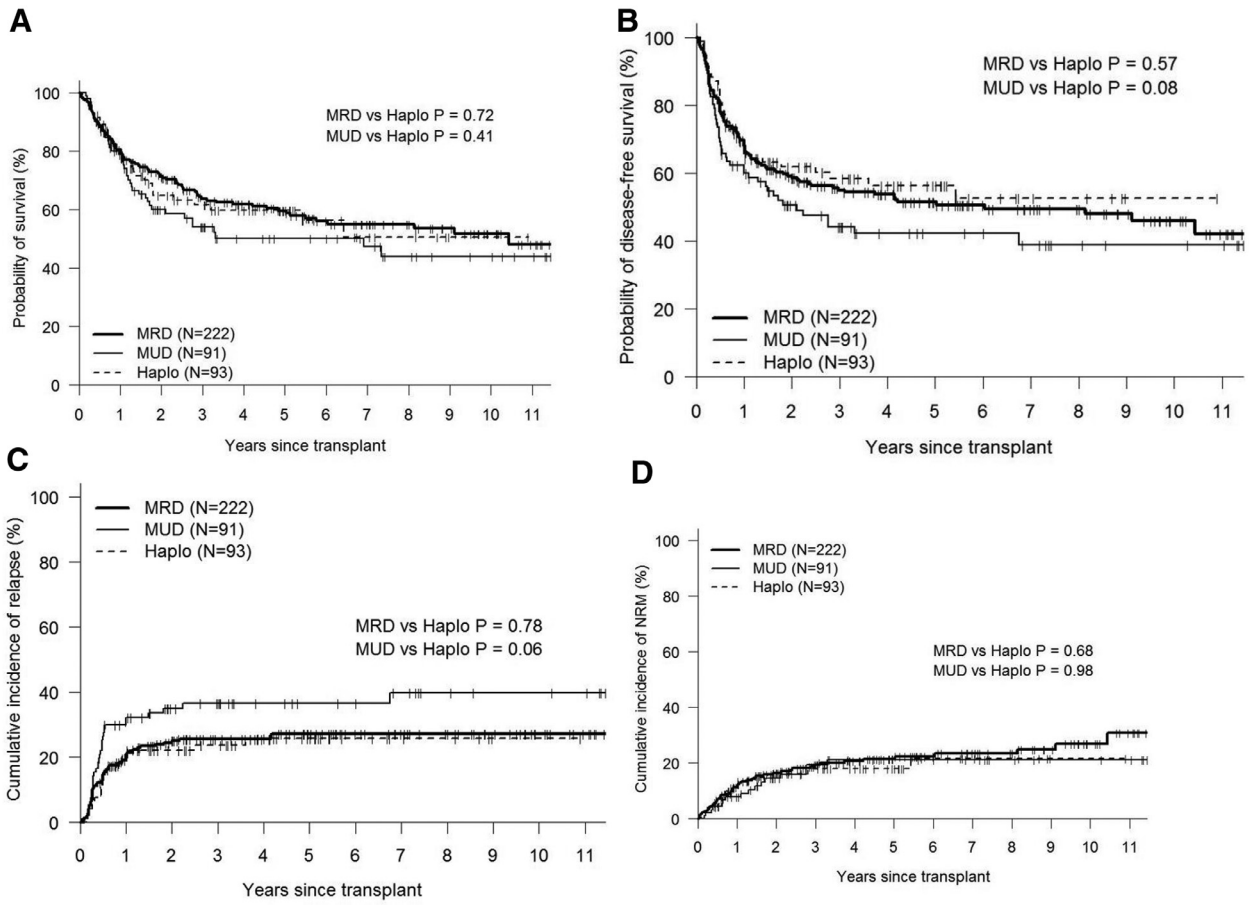

Figure 1. Survival probability and cumulative incidence of relapse. (A) Probability of OS. (B) Probability of DFS. (C) Cumulative incidence of relapse. (D) Cumulative incidence of NRM.

Table 3
Incidence of Acute GVHD at 100 Days and 180 Days

Outcome	Donor Source	100 d	180 d
		Estimate (95% CI)	Estimate (95% CI)
Grade 2-4 acute GVHD	MRD ≥35	22 (18-26)	24 (20-28)
	MUD ≥35	48 (40-56)	56 (48-64)
	Haplo <35	34 (27-42)	39 (31-47)
Grade 3-4 acute GVHD	MRD ≥35	6 (4-9)	7 (4-10)
	MUD ≥35	18 (12-24)	19 (13-26)
	Haplo <35	10 (5-17)	10 (5-17)

DISCUSSION

This is a single-center, retrospective study that compared the outcomes of 406 consecutive patients after MRDT or MUDT from donor graft source ≥35 years with HIDT recipients from a young donor graft source (<35 years of age) between 2005 and 2016. Our 3-year time point univariate analysis demonstrated DFS was similar in HIDT recipients compared with MUDT recipients (58% versus 44%, $P = .0695$) and MRDT recipients (58% versus 55%, $P = .600$). The recipients of a HIDT from a young donor source had better 3-year relapse rates compared with MUDT recipients (24% versus 37%, $P = .048$) with similar OS. HIDT recipients had a significantly lower cumulative incidence of grade 2 to 4 acute GVHD compared with MUDT recipients ($P = .009$) and a significantly lower moderate to severe cGVHD compared with both MUDT ($P = .010$) and MRDT ($P = .014$) recipients. The donor choice had no impact on OS, DFS, relapse, and TRM in multivariable analysis.

Strengths of this analysis include a relatively large number of patients using consistent supportive care algorithms and standardized grading of acute GHVD and cGVHD by a single dedicated nurse. The study is limited because of its retrospective nature, heterogeneity between conditioning regimens, difference in graft sources, and variation in GVHD prophylaxis. The GVHD prophylaxis for all HIDT recipients included post-transplant cyclophosphamide, which was not used for MRDT and MUDT recipients. The difference in GVHD prophylaxis may have a significant contribution to our findings and should be interpreted in the setting of the current standards of GVHD prophylaxis. An isolated graft source effect can only be elucidated in the setting of the same GVHD prophylaxis, which does not apply to our population.

Criteria for the selection of the most appropriate transplant donor, especially when faced with multiple graft sources, remain an area of ongoing debate. Our data are consistent with previously described literature regarding similar OS rates of HIDT, MRDT, and MUDT patients [6,8-10]. However, in the context of this study, we demonstrated that HIDT from donors ≤35 years of age had lower rates of cGVHD and better cGRFS compared with MRDTs or MUDTs from donors ≥35 years of age [6,8-10]. Furthermore, HIDT patients had lower relapse rates and similar DFS compared with MUDT patients.

Previous reports have indicated that advanced age of unrelated donors is an independent risk factor associated with unfavorable transplant outcomes [11,12,19]. In 2001, a large National Marrow Donor Program registry study of MUDT patients revealed transplants from donors >46 years of age

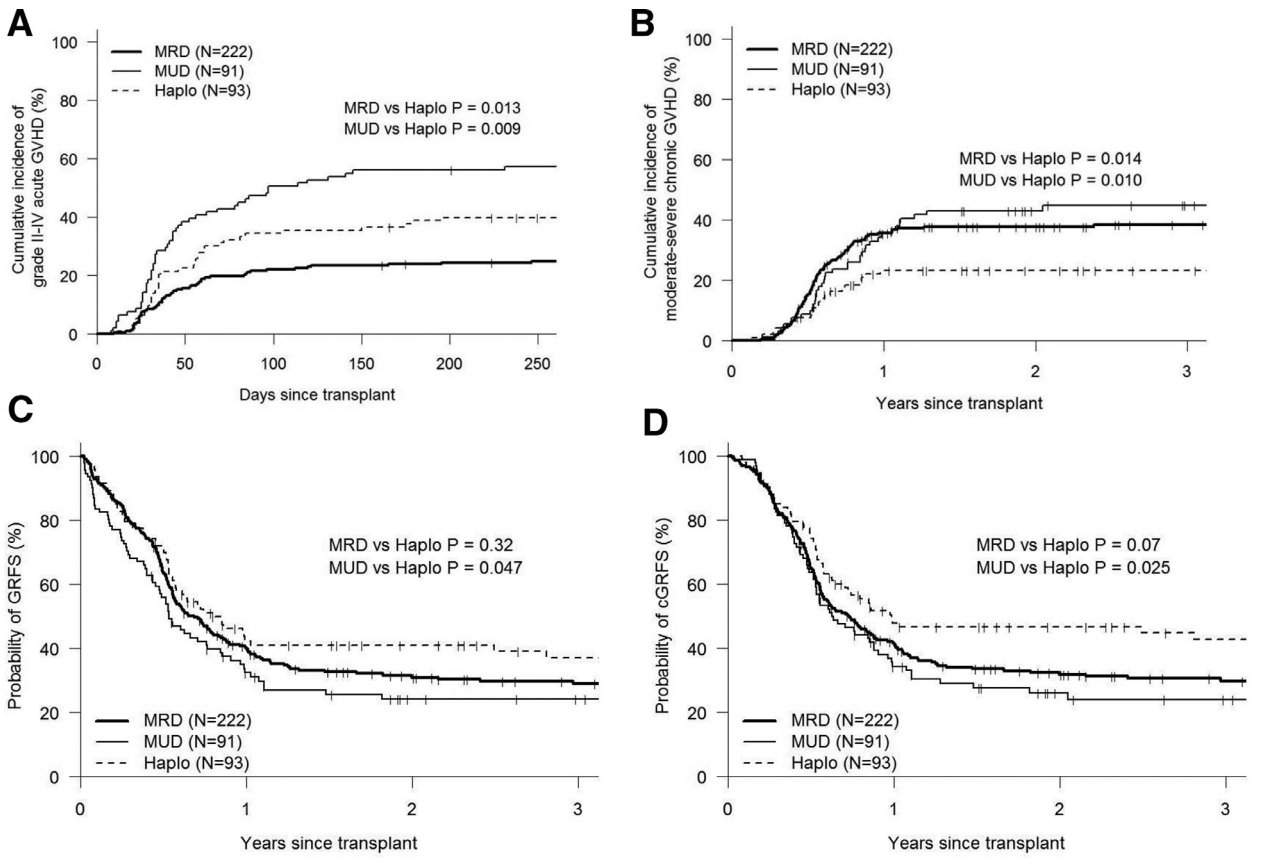

Figure 2. Cumulative incidence of acute GVHD and cGVHD and probability of GRFS and cGRFS. (A) Grade 2 to 4 acute GVHD. (B) Moderate to severe cGVHD. (C) Probability of GRFS. (D) Probability of cGRFS.

Table 4
Multivariate Analysis with Donor Type

Outcome	MRD ≥35 yr versus Haplo <35 yr			MUD ≥35 yr versus Haplo <35 yr		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
OS*	0.71	0.47-1.09	.120	0.94	0.58-1.53	.809
DFS†	0.96	0.66-1.41	.847	1.36	0.89-2.09	.157
Relapse‡	0.87	0.53-1.45	.597	1.54	0.88-2.69	.129
NRM§	1.07	0.60-1.90	.813	1.08	0.54-2.16	.836

* Model for OS also included recipient age, race, DRI, and CMI: comorbidity index.
† Model for DFS also included recipient age and DRI.
‡ Model for relapse also included DRI and year of transplantation.
§ Model for NRM also included recipient age, diagnosis, and CMI.

were associated with inferior OS and DFS and increased incidences of cGVHD [12]. Evidence from a more recent National Marrow Donor Program registry study in a similar patient population did not show an effect of donor age on OS; however, there was an association of higher NRM and both acute GVHD and cGVHD with donors >50 years of age [11]. The authors attributed the difference in OS compared with the previous registry study to improved donor-recipient HLA matching in more recent years [11]. These findings were in line with the results of our study.

The outcomes of donor age on HIDT were examined by several groups [16,19,20]. For example, a study conducted by Wang et al. [16] investigated the impact of donor characteristics on the outcomes of HIDT in 1210 patients with hematologic malignancies. HIDTs with older donors >30 years of age were associated with an increased incidence of acute GVHD, NRM, and inferior OS compared with patients who received HIDTs from donors <30 years of age [16]. These data are consistent with the data we reported in this study, but there are some differences that are important to note. First, the median recipient age in this study was 25 years, whereas the median age in our patient population was 54 years. This suggests that donor age may have more of an impact on HIDT outcomes than the recipient age. Evidence of this may be extrapolated from a study conducted in older adults who received nonmyeloablative HIDT with high-dose post-transplant cyclophosphamide [7]. The authors reported no statistically significant difference with NRM, relapse, or survival when they compared patients aged 60 to 69 years with patients who were 70 to 78 years of age [7]. Recently, Canaani et al. [21] conducted a retrospective analysis of a multinational registry examining the impact of donor age on transplant outcomes in 1270 patients who received a HIDT for acute leukemia. They reported patients older than 40 years with donors older than

40 years had an increase in NRM (HR, 1.86; 95% CI, 1.18 to 2.94; $P = .007$) and inferior OS (HR, 1.74; 95% CI, 1.22 to 2.47; $P = .002$). In this same patient population, older donor age did not affect outcomes when the transplant donor source was a sibling; however, if the donor was the patient's child and >35 years of age, he or she experienced inferior NRM, DFS, OS, and GVHD-free/relapse-free survival rates [21].

Despite evidence of improved transplantation outcomes with younger donors, the pathophysiology has yet to be elucidated. Studies have suggested an age-associated change in the cells of the immune system primarily changes to B cells, innate immune cells, and T cells [22,23]. Increased rates of GVHD seen in patients receiving HSCT from older donors may be caused by the change that occurs in T cell populations with age. Thymic involution leads to a decline in T cell proliferation and the naive T cell population and an increase in memory T cells [22]. The accumulation of senescent memory T cells is associated with an increased proinflammatory state and decreased levels of T regulatory cells [22].

Our study suggests when given the choice between a young, haploidentical relative donor or an older matched unrelated donor, it may be reasonable to select the young haploidentical relative donor to achieve similar survival outcomes and significantly lower rates of cGVHD.

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