ARTICLE

Alternative donor transplantation for acute myeloid leukemia in patients aged ≥50 years: young HLA-matched unrelated or haploidentical donor?

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ABSTRACT

We sought to study whether survival after haploidentical transplantation is comparable to that after matched unrelated donor transplantation for 822 patients aged 50-75 years with acute myeloid leukemia in first or second complete remission. One hundred and ninety-two patients received grafts from haploidentical donors (sibling 25%; offspring 75%) and 631 patients from matched unrelated donors aged 18-40 years. Patients' and disease characteristics of the two groups were similar except that recipients of matched unrelated donor transplantation were more likely to have poor risk cytogenetics and more likely to receive myeloablative conditioning regimens. Time from documented remission to transplant did not differ by donor type. Five-year overall survival was 32% and 42% after haploidentical and matched unrelated donor transplant, respectively (P=0.04). Multivariable analysis showed higher mortality (hazard ratio 1.27, P=0.04) and relapse (hazard ratio 1.32, P=0.04) after haploidentical transplantation, with similar non-relapse mortality risks. Chronic graft-*versus*-host disease was higher after matched unrelated donor compared to haploidentical transplantation when bone marrow was the graft (hazard ratio 3.12, P<0.001), but when the graft was peripheral blood, there was no difference in the risk of chronic graft-*versus*-host disease between donor types. These data support the view that matched unrelated donor transplant with donors younger than 40 years is to be preferred.

Introduction

Standard post-remission therapy for eligible patients with high risk or relapsed acute myeloid leukemia (AML), including older patients, is an allogeneic

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hematopoietic cell transplant from a matched sibling or an alternative donor such as a haploidentical or unrelated donor. The introduction of transplantation of T-cell replete bone marrow or peripheral blood from a haploidentical relative using post-transplant cyclophosphamide for graft-*versus*-host disease (GvHD) has gained broad acceptance with consistently favorable outcomes.[1-5] Others have reported comparable outcomes after haploidentical donor compared to unrelated donor transplantation for AML.[6-8] Yet in a recent report from the Center for International Blood and Marrow Transplant Research (CIBMTR) and the European Society for Blood and Marrow Transplant (EBMT), non-relapse mortality and overall mortality were higher after transplantation of grafts from haploidentical (offspring) donors compared to HLA-matched siblings for AML and acute lymphoblastic leukemia (ALL) in patients aged 55-76 years.[9] An earlier study of allogeneic transplantation for older patients with hematologic malignancy concluded HLA-matched sibling donor transplants was associated with lower GvHD and better survival in patients with good performance scores compared to HLA-matched unrelated donor (MUD) who were younger than their recipients.[10] Published reports have recorded better survival after transplantation of bone marrow or peripheral blood grafts from unrelated adult donors aged ≤40 years.[11] Thus with increasing numbers of transplants being performed for AML in older patients (≥50 years), a clinically relevant question is whether to use a haploidentical relative or a young MUD when considering alternative donor transplantation.

Methods

Patients

Data are reported to the CIBMTR from 195 transplant centers in the United States and 90 of these centers contributed data for the current analysis. Patients are followed longitudinally until death or lost to follow up. Eligible patients were aged 50-76 years with AML, transplanted in first or second remission in the United States between 2008 and 2015 and with commonly used conditioning regimens (*Online Supplementary Table S1*). Patients received bone marrow or peripheral blood from a haploidentical donor (sibling or offspring mismatched at ≥ 2 HLA loci) or an 8/8 HLA-matched MUD aged 18-40 years. Unrelated donors aged >40 years were excluded as over 90% of unrelated donors selected for recent transplants in the US are aged 18-40 years old.[11] Excluded patients included those transplanted in relapse (n=248) and receiving transplant regimens that included anti-thymocyte globulin or alemtuzumab (n=76) or CD34 selected peripheral blood (n=56) or *ex vivo* T-cell depletion (n=34). Patients provided written informed consent for research. The Institutional Review Board of the National Marrow Donor Program approved this study.

End points

The primary end point was overall mortality. Death from any cause was considered an event and surviving patients were censored at last follow up. Relapse was defined as the first detection of one of the following: hematologic, cytogenetic or molecular leukemia recurrence, and non-relapse mortality was defined as death in remission. Treatment failure was defined as relapse or death (inverse of leukemia-free survival). Neutrophil recovery was defined as the first of three consecutive days of an achieved absolute neutrophil count ≥$0.5x10^9$/L and platelet recovery was defined as the first date of an achieved platelet count ≥$20x10^9$/L after seven consecutive days of no platelet transfusions. Grade II-IV acute GvHD and chronic GvHD were based on reports from each transplant center using standard criteria.[12,13]

Statistical analysis

Differences in patients', disease and transplant characteristics between the two groups (i.e. donor type) were compared using the χ^2 statistic for categorical variables. The probabilities of overall survival and leukemia-free survival were calculated using the Kaplan-Meier estimator.[14] The probabilities of neutrophil and platelet recovery, acute and chronic GvHD, non-relapse mortality and relapse were calculated using the cumulative incidence estimator to accommodate competing risks.[15] Cox regression models were built to study the effect of donor type (MUD *vs.* haploidentical) and other factors associated with overall mortality, grade II-IV acute GvHD, chronic GvHD, relapse, non-relapse mortality and treatment failure.[16] Variables tested included: donor age (tested as a continuous variable), recipient age, sex, performance score, hematopoietic cell transplant co-morbidity (HCT-CI) score, cytomegalovirus (CMV) serostatus, disease status, cytogenetic risk, transplant conditioning regimen intensity and transplant period. All variables that attained P≤0.05 were held in the final multivariable model with the exception of the variable for donor type that was held in all steps of model building and the final model regardless of level of significance. There was no first order interaction between donor type and other variables including conditioning regimen intensity. Transplant center effect on survival was tested using the frailty approach.[17] All P-values are two-sided. All analyses were made using SAS version 9.4 (Cary, NC, USA).

Results

Patients', disease and transplant characteristics

Characteristics of recipients of haploidentical (n=192) and MUD (n=631) transplants were similar except that recipients of haploidentical transplants were more likely to have favorable or intermediate risk cytogenetics (P=0.03), and to have received reduced intensity conditioning regimen (P<0.0001) (Table 1). The predominant reduced intensity conditioning regimen for haploidentical transplantation was low-dose total body irradiation (200 cGy), cyclophosphamide (29 mg/kg) and fludarabine (150 mg/m^2). The predominant reduced intensity conditioning regimen for MUD transplantation was busulfan or melphalan with fludarabine. The median ages of recipients of haploidentical and MUD transplantations were 61 and 61 years, respectively. The median time to haploidentical transplantation from diagnosis for patients in CR1 and CR2 were 5 and 20 months, respectively. The corresponding time to MUD transplantation was 5 and 18 months. Bone marrow was the predominant graft for haploidentical transplants and peripheral blood the predominant graft for MUD transplants. All recipients of haploidentical transplantation received a uniform GvHD prophylaxis regimen: post-transplant cyclophosphamide with a calcineurin inhibitor and mycophenolate. Recipients of MUD transplantation received a calcineurin inhibitor containing GvHD prophylaxis; calcineurin inhibitor with methotrexate was the predominant regimen. Haploidentical donors (25% siblings and 75% offspring) were mismatched at ≥2 HLA-loci and the median donor age was 37 years (range: 17-69). MUD were allele-level matched at HLA-A, -B, -C and -DRB1 and their median age was 27 years (range 18-40). The median follow up of

Table 1. Patients', disease and transplant characteristics.

Variable	Haploidentical donor	Unrelated donor	*P*
Number	192	631	
Age, years			0.7
50 – 59	85 (44%)	266 (42%)	
60 – 69	89 (46%)	312 (49%)	
70 – 79	18 (9%)	53 (8%)	
Sex, male/female	104 (54%)/88 (46%)	356 (56%)/275 (44%)	0.6
Performance score			<0.001
90 – 100	114 (59%)	384 (61%)	
≤ 80	67 (35%)	241 (38%)	
Not reported	11 (6%)	6 (<1%)	
HCT- comorbidity index			0.1
0 – 2	108 (56%)	310 (49%)	
≥3	84 (44%)	317 (50%)	
Not reported	–	4 (<1%)	
Cytomegalovirus serostatus			0.7
Negative	63 (33%)	220 (35%)	
Positive	128 (67%)	405 (64%)	
Not reported	1 (<1%)	6 (<1%)	
Disease status			0.03
First complete remission	146 (76%)	524 (83%)	
Second complete remission	46 (24%)	107 (17%)	
Cytogenetic risk			0.03
Favorable	8 (4%)	20 (3%)	
Intermediate	148 (77%)	425 (67%)	
Poor	35 (18%)	176 (28%)	
Not reported	1 (<1%)	10 (2%)	
Conditioning regimen			<0.001
Myeloablative			
Busulfan/cyclophosphamide	25 (13%)	108 (17%)	
Busulfan/fludarabine	3 (1%)	171 (27%)	
TBI + other agents	19 (10%)	–	
Reduced intensity			
Busulfan/fludarabine	–	234 (37%)	
Melphalan/fludarabine	10 (5%)	118 (18%)	
TBI/cyclophosphamide/fludarabine	124 (65%)	–	
TBI + other agents	11 (6%)	–	
Graft type			<0.001
Bone marrow	132 (69%)	96 (15%)	
Peripheral blood	60 (31%)	535 (85%)	
Donor-recipient relationship/HLA-match			
Haploidentical sibling	48 (25%)	–	
Offspring	144 (75%)	–	
HLA match: A, B, C, DRB1	–	631 (100%)	
Donor age, median (range)	37 (16–69)	27 (18–40)	<0.001
Transplant period			0.007
2008 – 2011	46 (24%)	216 (34%)	
2012 – 2015	146 (76%)	415 (66%)	
Median follow up of survivors months (range)	42 (12–97)	47 (5–124)	

HCT: hematopoietic cell transplant; TBI: total body irradiation.

recipients of haploidentical and MUD transplantations were 42 months (range 12-97) and 47 months (range 5-124), respectively.

Overall mortality

The risks for overall mortality was higher after transplantation of bone marrow or peripheral blood from haploidentical compared to MUD after adjusting for HCT-CI score and cytogenetic risk (Table 2 and Figure 1A). Overall mortality risks were higher in patients with a HCT-CI score of 3 or higher compared to score 0-2 (HR 1.39, 95%CI: 1.14-1.68; *P*=0.001) and poor risk cytogenetics compared to intermediate/good risk cytogenetics (HR 1.46, 95%CI: 1.18-1.81; *P*=0.001). Donor age was not associated with overall mortality (HR 1.00, 95%CI: 0.98-1.01; *P*=0.9). In a subset analysis limited to patients in CR1, overall mortality risk was also higher after haploidentical compared to MUD transplant (HR 1.31, 95%CI: 1.01-1.70; *P*=0.05). Although transplant conditioning regimen intensity was not associated with mortality risk (HR 0.88, 95%CI: 0.72-1.08; *P*=0.2), we tested for an interaction between donor type and conditioning regimen intensity and found none (*P*=0.7). An effect of transplant center on overall mortality was explored and none was found.

Causes of death differed by donor type (*P*=0.01); recurrent disease was the most common cause of death in both treatment groups although this was higher after haploidentical (59%) compared to MUD (54%) transplants. Only 2% of deaths after haploidentical transplant was attributed to GvHD compared to 14% after MUD transplant. There were no differences in proportion of deaths attributed to graft failure, infection, interstitial pneumonitis or organ failure by donor type.

Hematopoietic recovery

The median times to neutrophil and platelet recovery after haploidentical and MUD transplantation was 17 *versus* 14 days for neutrophils (*P*<0.001) and 26 *versus* 17 days for platelets (*P*<0.001). The day-28 rates of neutrophil recovery were 89% (95%CI: 84-93) and 98% (95%CI: 97-99) (*P*<0.001) and the day-100 rates of platelet recovery 89% (95%CI: 84-93) and 96% (95%CI: 95-98) (*P*=0.004) after haploidentical and MUD transplantation, respectively. The 1-year cumulative incidence of primary or secondary graft failure after haploidentical and MUD transplantation were 11% (95%CI: 7-16) and 9% (95%CI: 7-11) (*P*=0.4).

Graft-*versus*-host disease

Compared to MUD transplantation, grade II-IV acute GvHD was significantly lower after haploidentical transplantation (HR 0.53, 95%CI: 0.38-0.75; *P*<0.001). Independent of donor type, grade II-IV acute GvHD was higher in patients with HCT-CI score of 3 or higher (HR 1.34, 95%CI: 1.06-1.69; *P*=0.01) and with myeloablative conditioning regimens (HR 1.42, 95%CI:1.14-1.79; *P*=0.003). The day-100 incidence of grade II-IV acute GvHD after haploidentical and MUD transplantation was 21% (95%CI: 15-27) and 35% (95%CI: 32-39), respectively (*P*<0.001). Chronic GvHD risk was higher after MUD compared to haploidentical donor transplantation when bone marrow was the graft (HR 3.12, 95%CI: 1.75-5.56; *P*<0.001). The 2-year probability of chronic GvHD following a bone marrow graft from a haploidentical donor was 15% (95%CI:10-22) compared to 36% (95%CI: 27-46) from a MUD (*P*<0.001). However, when the graft was peripheral blood, there was no difference in risk of chronic GvHD by donor type (HR 1.08, 95%CI: 0.71-1.69; *P*=0.7). The 2-year probabilities of chronic GvHD following a peripheral blood graft from haploidentical and MUD were 46% (95%CI: 31-60) and 55% (50-59), respectively (*P*=0.3). Among patients who developed chronic GvHD, its severity differed by donor type; extensive chronic GvHD was reported in 74% of haploidentical compared to 88% of MUD transplant recipients (*P*=0.01).

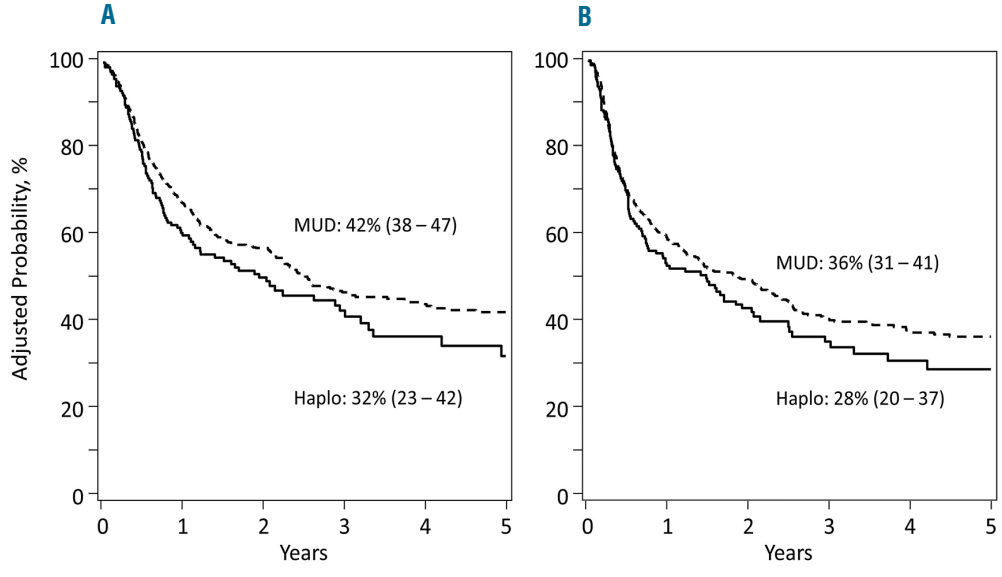

Figure 1. 5-year adjusted probability of overall survival (OS). (A) OS: the 5-year adjusted probability of OS after transplantation of grafts from haploidentical (Haplo) donor (32%, 95%CI: 23-42) and matched unrelated donor (MUD) (42%, 95%CI: 38-47). (B) Leukemia-free survival: the 5-year adjusted probability of disease-free survival after transplantation of grafts from Haplo donor (28%, 95%CI: 20-37) and MUD (36%, 95%CI: 31-41).

Treatment failure

There were no differences in treatment failure by donor type (Table 2 and Figure 1B). Independent of donor type, treatment failure was higher in patients with HCT-CI score of ≥3 (HR 1.28, 95%CI: 1.06-1.53; *P*=0.009) and those with poor cytogenetic risk (HR 1.56, 95%CI: 1.27-1.90; *P*<0.001). Donor age was not associated with treatment failure (HR 0.99, 95%CI: 0.98-1.01; *P*=0.8). In a subset analysis limited to transplantation in CR1, there were no differences in treatment failure by donor type (HR 1.22, 95%CI: 0.95-1.56; *P*=0.1).

Non-relapse mortality and relapse

Non-relapse mortality risk did not differ by donor type (Table 2 and Figure 2A). Independent of donor type, non-relapse mortality was higher for HCT-CI score of >3 (HR 1.40, 95%CI: 1.03-1.90; *P*=0.03). Relapse occurred in 299 patients. Of the 299 patients who relapsed, two (<1%) patients had only molecular relapse, 80 (27%) only cytogenetic relapse, 56 (19%) hematologic relapse, 59 (20%) molecular and hematologic relapse, and 102 (34%) cytogenetic and hematologic relapse. Relapse was higher after transplantation from haploidentical donors compared to MUD (Table 2 and Figure 2B). Independent of donor type, the risk of relapse was higher with poor risk cytogenetics (HR 1.82, 95%CI: 1.43-2.33; *P*<0.001). Donor age was not associated with non-relapse mortality (HR 1.01, 95%CI: 0.98-1.03; *P*=0.5) or relapse (HR 0.99, 95%CI: 0.98-1.01; *P*=0.4).

Table 2. Effect of donor type on transplant outcomes.

Outcome	Number Events/Evaluable	Hazard Ratio (95% confidence interval)	*P*
Overall mortality			
Unrelated donor	316/631	1.00	
Haploidentical donor	100/192	1.27 (1.01 – 1.60)	0.04
Non-relapse mortality			
Unrelated donor	135/624	1.00	
Haploidentical donor	36/191	1.01 (0.70 – 1.46)	0.9
Relapse			
Unrelated donor	224/624	1.00	
Haploidentical donor	75/191	1.32 (1.01 – 1.72)	0.04
Treatment failure			
Unrelated donor	359/624	1.00	
Haploidentical donor	111/191	1.19 (0.96 – 1.49)	0.1

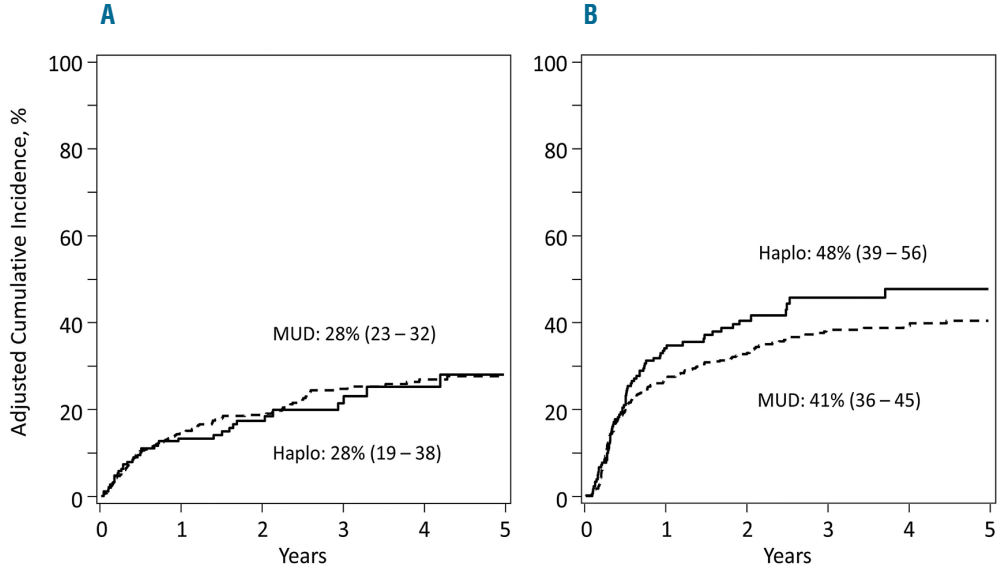

Figure 2. 5-year adjusted cumulative incidences of relapse and non-relapse mortality (NRM). (A) NRM: the 5-year adjusted cumulative incidence of NRM after transplantation of grafts from haploidentical (Haplo) donor (28%, 95%CI: 19-38) and matched unrelated donor (MUD) (28%, 95%CI: 19-38). (B) Relapse: the 5-year adjusted cumulative incidence of relapse after transplantation of grafts from Haplo donor (48%, 95%CI: 39-56) and MUD (41%, 95%CI: 36-45).

Discussion

Acute myeloid leukemia remains one of the main indications for allogeneic stem cell transplantation, and with an aging population, it is expected that both the incidence of AML and the number of transplants in older patients with AML will increase.[18] Furthermore, recent trends also show an increase in haploidentical transplants with use of post-transplant cyclophosphamide for GvHD prophylaxis. Although an earlier CIBMTR report showed no difference in survival after haplo-identical and MUD transplantation, transplant outcomes in patients older than 50 years were not analyzed as a separate cohort.[6] In the setting of HLA-matched sibling donor transplantation for patients older than 50 years with hematologic malignancy, survival was higher compared to MUD transplants with donors aged <50 years in patients with performance scores of 90 or 100.[10] In those with performance scores 80 or lower, there were no significant differences in survival by donor type.[10] With the increasing use of haplo-identical donors for AML, the current analysis sought to study whether survival after haploidentical donor transplantation would be better compared to transplantation of grafts from a young MUD (donor age 18-40 years). The results showed a survival advantage after MUD transplantation that can be attributed to lower relapse risks. Our findings lend support to our hypothesis that a young MUD should be the donor of choice when available. Furthermore, the data presented here suggest comparable times to transplantation in both treatment groups, confirming timely access to unrelated donors is no longer a barrier.

The prognostic significance of donor age and donor-recipient HLA match in the setting of unrelated donor transplantation has been confirmed in several reports, including a recent report that concluded there was a 5.5% increase in the hazard ratio for overall mortality for every 10-year increment in the age of the donor.[11,19] The observed excess mortality with increasing donor age was attributed to higher non-relapse mortality and not leukemia recurrence.[11] In contrast, the effect of donor age for haplo-identical transplants is mixed. In a relatively young population with hematologic malignancy that predominantly used parental donors, a male donor under 30 years of age was associated with best survival.[20] On the other hand, for adults with hematologic malignancy, neither donor-recipient relationship or donor age was associated with transplant outcomes. In the current analysis, the better HLA-matching between the recipient and the unrelated donor may have also improved survival after MUD transplantation. Higher survival was recorded after HLA-matched sibling compared to haploidentical transplant for patients with acute leukemia who were older than 55 years confirming the importance of HLA matching for allogeneic transplantation.[9]

Unlike other reports that compared haploidentical to MUD or HLA-matched sibling transplants, relapse risks after MUD transplants were lower in the current analysis after adjusting for cytogenetic risk, transplant conditioning intensity and graft type.[6-9] Predictably, relapse was higher in patients with poor risk cytogenetics, in recipients of reduced intensity conditioning regimens, and after transplantation of bone marrow.[21] The recent Blood and Marrow Transplant Clinical Trials Network trial, BMT CTN 0901, showed higher relapse in patients with AML conditioned with reduced intensity regimens and was consistent with other reports demonstrating the benefit of myeloablative regimens for AML.[22] Furthermore, a recent CIBMTR report on graft type and haploidentical transplants demonstrated lower relapse risks with peripheral blood compared to bone marrow, but without a survival advantage.[5] Consistent with clinical practice, recipients of haploidentical transplants were more likely to receive bone marrow and reduced intensity conditioning regimen. Therefore, we carefully addressed the effect of conditioning regimen intensity (P=0.2) and graft type (P=0.6) in the model for survival and found none. Nevertheless, it is plausible that the observed higher relapse risk associated with haploidentical transplantation may, in part, be attributed to the low-dose TBI, cyclophosphamide and fludarabine regimen, the predominant regimen for haploidentical transplants in the current analysis. As shown by others, we found that both acute and chronic GvHD were lower in recipients of haploidentical transplantation.[5] The decreased risk of chronic GvHD, however, was restricted to the recipients of bone marrow graft. As the use of peripheral blood increases in haploidentical transplants, we will likely observe increased rates of chronic GvHD.[5] This remains a significant consideration, particularly in the older patient where the morbidity and impact on quality of life associated with chronic GvHD can be significant.[23-25]

The current analysis has several limitations related to the use of data reported to an observation registry. First, we are unable to study donor choices and it is possible that some transplant centers prioritize the selection of a haploidentical donor. Second, we are unable to properly separate the effect of conditioning regimen and graft type, as these factors are confounded with donor type. Third, while every attempt was made to adjust for the observed difference in survival, there may be several unknown or unmeasured factors we could not consider. Finally, it should be noted that we did not observe a center effect, although fewer centers performed haploidentical transplants.

While the use of haploidentical transplantation with post-transplant cyclophosphamide is increasing rapidly, and several early studies suggest similar outcomes to patients transplanted with matched related or unrelated donors, it remains important to analyze outcomes in specific patient populations and diseases. In the current analysis, with its focus on patients aged 50 years or older with AML in first or second remission, we observed higher mortality after haploidentical compared to MUD transplantation with donors younger than 40 years. We acknowledge donor selection is ideally studied in the setting of a controlled clinical trial. However, the disparate availability of MUD and related haploidentical donors remains a challenge, and attempts to study outcomes of donor choice both retrospectively and prospectively may be necessary.

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