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Outcomes of haploidentical vs matched sibling transplantation for acute myeloid leukemia in first complete remission

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HLA-haploidentical hematopoietic cell transplantation (Haplo-HCT) using posttransplant cyclophosphamide (PT-Cy) has improved donor availability. However, a matched sibling donor (MSD) is still considered the optimal donor. Using the Center for International Blood and Marrow Transplant Research database, we compared outcomes after Haplo-HCT vs MSD in patients with acute myeloid leukemia (AML) in first complete remission (CR1). Data from 1205 adult CR1 AML patients (2008-2015) were analyzed. A total of 336 patients underwent PT-Cy–based Haplo-HCT and 869 underwent MSD using calcineurin inhibitor–based graft-versus-host disease (GVHD) prophylaxis. The Haplo-HCT group included more reduced-intensity conditioning (65% vs 30%) and bone marrow grafts (62% vs 7%), consistent with current practice. In multivariable analysis, Haplo-HCT and MSD groups were not different with regard to overall survival ($P = .15$), leukemia-free survival ($P = .50$), nonrelapse mortality ($P = .16$), relapse ($P = .90$), or grade II-IV acute GVHD ($P = .98$). However, the Haplo-HCT group had a significantly lower rate of chronic GVHD (hazard ratio, 0.38; 95% confidence interval, 0.30-0.48; $P < .001$). Results of subgroup analyses by conditioning intensity and graft source suggested that the reduced incidence of chronic GVHD in Haplo-HCT is not limited to a specific graft source or conditioning intensity. Center effect and minimal residual disease–donor type interaction were not predictors of outcome. Our results indicate a lower rate of chronic GVHD after PT-Cy–based Haplo-HCT vs MSD using calcineurin inhibitor–based GVHD prophylaxis, but similar other outcomes, in patients with AML in CR1. Haplo-HCT is a viable alternative to MSD in these patients.

## Methods

### Data sources

The Center for International Blood and Marrow Transplant Research (CIBMTR) includes data from a voluntary working group of >450 transplant centers worldwide that contributes detailed data on allogeneic and autologous HCT. Participating centers are required to report all transplants consecutively; compliance is monitored by on-site audits, and patients are followed longitudinally. Computerized checks for discrepancies, physicians’ review of submitted data, and on-site audits of participating centers ensure data quality. Studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. Protected health data is protected in accordance with Health Insurance Portability and Accountability Act (HIPAA) requirements.

## Data Quality

A central requirement of the CIBMTR is the protection of research participants. All data entered into the CIBMTR database are protected according to federal, state, and institutional regulations. The CIBMTR requires all participating centers to follow the guidelines of the Health Insurance Portability and Accountability Act (HIPAA). Protected health data is protected in accordance with HIPAA requirements.

## Statistical Analysis

Our results indicate a lower rate of chronic GVHD after PT-Cy–based Haplo-HCT vs MSD using calcineurin inhibitor–based GVHD prophylaxis, but similar other outcomes, in patients with AML in CR1. Haplo-HCT is a viable alternative to MSD in these patients.
information used in the performance of such research is collected and maintained in CIBMTR’s capacity as a Public Health Authority under the HIPAA Security Rule. The CIBMTR collects data at 2 levels: the transplant essential data (TED) level and the comprehensive report form (CRF) level. The TED-level data are an internationally accepted standard data set that contains a limited number of key variables for all consecutive transplant recipients. Details on CRF- and TED-level data collection have been published previously and are described in detail elsewhere.17 TED- and CRF-level data are collected pretransplant, 100 days and 6 months posttransplant, annually until year 6 posttransplant, and biannually thereafter until death.

Patients
We included all adult patients (age ≥18 years) with AML who were in CR1 at the time of their first allogeneic HCT (between 2008 and 2015) using an MSD or a haploidentical related donor (mismatched for ≥2 HLA loci among HLA-A, HLA-B, HLA-C, and HLA-DRB1). In the Haplo-HCT group, only cases receiving PT-Cy–based GVHD prophylaxis (with or without a calcineurin inhibitor [CNI] and mycophenolate mofetil) were included, whereas in the MSD group, GVHD prophylaxis was limited to CNI-based approaches. Patients receiving ex vivo (T-cell depleted or CD34-selected grafts) or in vivo (eg, anti-thymocyte immunoglobulin) graft manipulation were excluded. Both peripheral blood and bone marrow as a graft source and myeloablative conditioning (MAC) and RIC regimens were included. The Institutional Review Board of the National Marrow Donor Program approved this study.

End points and definitions
The primary end point was OS. Secondary end points were hematopoietic recovery, relapse, LFS, NRM, and acute and chronic GVHD. OS was defined as the time from HCT to death from any cause. LFS was defined as survival with no evidence of relapse or progression. Relapse was defined as the reappearance of ≥5% blasts on morphological evaluation in bone marrow or an extramedullary site. NRM was defined as death without evidence of relapse or progression. Acute and chronic GVHD were defined according to standard criteria.18 Neutrophil engraftment was defined as achieving an absolute neutrophil count ≥ 0.5 × 10^9/L for 3 consecutive days, and platelet engraftment was defined as a platelet count ≥ 20 × 10^9/L for 7 days unsupported by transfusion.

Cytogenetic risk was defined according to SWOG classification.19 Minimal residual disease (MRD) information before HCT was not collected consistently or reported to the CIBMTR during the period of this study. However, given its key importance in HCT outcomes,20 we used all relevant reported variables to generate an estimate for MRD before HCT (supplemental Table 1). We classified a patient as MRD positive in the following scenarios pre-HCT: (1) answer was “no” to questions on cytogenetic, molecular, or flow cytometry-based remission; (2) answer was “yes” to the question on disease detectability in the blood or bone marrow by flow cytometry; or (3) answer was “yes” to the presence of molecular markers, such as CEBPA, FLT3 D835, FLT3-ITD, IDH1, IDH2, KIT, or NPM1 mutation. We classified a patient as MRD negative if they were not classified as MRD positive and (1) answer was “no” to the question on disease detectability in the blood or bone marrow by flow cytometry or (2) answer was “yes” to questions on cytogenetic, molecular, or flow cytometry-based remission. HCT comorbidity index (HCT-CI) was defined according to standard criteria.21

Statistical methods
Patient- and transplant-related variables were compared using the χ² test for categorical variables and the Mann-Whitney U test for continuous variables. Kaplan-Meier curves were used to estimate the probability of OS and LFS. Cumulative incidence was used to estimate the probability of NRM, GVHD, and relapse. For GVHD and relapse, NRM was treated as a competing risk. For NRM, relapse was treated as a competing risk. For LFS and OS, patients were censored at the time of last follow-up.

Univariate analysis was performed for the main effect (donor type) in relation to outcomes. In multivariable Cox proportional-hazards models, donor type (main effect) was forced in, and a backward stepwise model selection approach using the Akaike information criterion was used to identify a priori selected potential predictors of outcomes (supplemental Table 2). Covariates significant at a 5% level were kept in the final model. The assumption of proportional hazards for each factor in the Cox model was tested by adding time-dependent covariates. Potential interactions between main effect and significant covariates were tested. Transplantation center effect was tested using the frailty model.22 Adjusted probabilities of LFS and OS, as well as adjusted cumulative incidence functions of NRM and relapse, were calculated using multivariable models, stratified on the main effect and weighted by the pooled sample proportion value for each prognostic factor.

We hypothesized that OS following PT-Cy–based Haplo-HCT is not significantly different from MSD using CNI-based GVHD prophylaxis in AML patients in CR1. Assuming that there is a ≥10% difference between the groups in 3-year OS, using a 2-sided test (allowing for the difference to be in either direction) at 5% significance level, and with the available sample size that we identified in the CIBMTR database, we had 86% power to detect this difference. All analyses were done using the statistical package SAS version 9.3 (SAS Institute, Cary, NC).

Results
Data from 1205 patients (Haplo-HCT, n = 336; MSD, n = 869) were analyzed. Patient, disease, and transplant characteristics are shown in Table 1. Patients were older and donors were younger in the Haplo-HCT group; 55% vs 38% of Haplo-HCT vs MSD recipients and 11% vs 35% of Haplo-HCT vs MSD recipients were ≥55 years of age (P < .001 for both comparisons). There were more African American patients in the Haplo-HCT group compared with the MSD group (21% vs 5%, P < .001). The Haplo-HCT group included more RIC (65% vs 30%, P < .001) and bone marrow grafts (62% vs 7%, P < .001), consistent with current practice. In addition, a smaller proportion of Haplo-HCT recipients were white (68% vs 84%, P < .001) and a smaller proportion underwent HCT within 6 months of diagnosis compared with the MSD group (69% vs 83%, P < .001). Intermediate-risk cytogenetics was more common in the MSD group (65% vs 50%, P < .001). As expected, a smaller proportion of Haplo-HCT vs MSD transplants were performed before 2011 (11% vs 49%, P < .001).
### Table 1. Patients, disease, and transplant characteristics

| Variable                        | Haplo (n = 336) | MSD (n = 869) | P     |
|---------------------------------|-----------------|---------------|-------|
| **Patient age, y**              |                 |               | <.001 |
| 18-54                           | 152 (45)        | 542 (62)      |       |
| ≥55                             | 184 (55)        | 327 (38)      |       |
| Median (range)                  | 57 (18-74)      | 52 (18-71)    |       |
| **Donor age, y**                |                 |               | <.001 |
| 18-54                           | 212 (63)        | 560 (64)      |       |
| ≥55                             | 37 (11)         | 306 (35)      |       |
| Missing                         | 87 (26)         | 3 (<1)        |       |
| Median (range)                  | 39 (16-68)      | 51 (18-73)    |       |
| **Sex**                         |                 |               | .42   |
| Male                            | 183 (54)        | 451 (52)      |       |
| Female                          | 153 (46)        | 418 (48)      |       |
| **Race**                        |                 |               | <.001 |
| White                           | 229 (68)        | 727 (84)      |       |
| African American                | 69 (21)         | 46 (5)        |       |
| Others                          | 20 (6)          | 70 (8)        |       |
| Missing                         | 18 (5)          | 26 (3)        |       |
| **HCT-CI**                      |                 |               | .20   |
| 0                               | 99 (29)         | 254 (29)      |       |
| 1                               | 53 (16)         | 136 (16)      |       |
| 2                               | 43 (13)         | 124 (14)      |       |
| ≥3                              | 133 (40)        | 309 (36)      |       |
| Missing                         | 8 (2)           | 46 (5)        |       |
| **Karnofsky performance status**|                 |               | .78   |
| <90                             | 112 (33)        | 308 (35)      |       |
| ≥90                             | 208 (62)        | 551 (64)      |       |
| Missing                         | 16 (5)          | 10 (1)        |       |
| **Time from diagnosis to HCT, mo** |             |               | <.001 |
| <6                              | 231 (69)        | 721 (83)      |       |
| 6-12                            | 89 (26)         | 131 (15)      |       |
| >12                             | 16 (5)          | 17 (2)        |       |
| Median (range)                  | 5 (2-36)        | 4 (1-18)      |       |
| **Type of AML**                 |                 |               | .05   |
| De novo                         | 244 (73)        | 662 (76)      |       |
| Transformed from MDS/MPN        | 70 (21)         | 133 (15)      |       |
| Therapy related                 | 22 (6)          | 74 (9)        |       |
| **Donor/recipient cytomegalovirus serostatus** | | | .26 |
| +/-                             | 139 (41)        | 328 (38)      |       |
| +/−                             | 29 (9)          | 98 (11)       |       |
| −/+                             | 91 (27)         | 223 (26)      |       |
| −/−                             | 75 (22)         | 204 (23)      |       |
| Missing                         | 2 (<1)          | 16 (2)        |       |
| **Donor/recipient sex**         |                 |               | .47   |
| Male-male                       | 114 (34)        | 256 (29)      |       |
| Male-female                     | 88 (26)         | 231 (26)      |       |
| Female-male                     | 69 (21)         | 195 (23)      |       |

Unless otherwise noted, all data are n (%).

Haplo, haploidentical; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm.

*All Haplo-HCT patients received PT-Cy, whereas all MSD patients received a CNI.*
Univariate analysis

**Acute and chronic GVHD.** In univariate analysis (Table 2), the Haplo-HCT group had similar rates of grade II-IV acute GVHD (32%; 95% confidence interval [95% CI], 27-37 vs 30%, 95% CI, 27-33; \( P = .64 \)) and grade III-IV acute GVHD (10%; 95% CI, 7-14 vs 12%; 95% CI, 10-14; \( P = .54 \)) at 6 months but lower rates of chronic GVHD (26%, 95% CI, 21-31 vs 56%; 95% CI, 53-60 at 3 years; \( P < .001 \)) and extensive chronic GVHD (16%; 95% CI, 12-20 vs 47%; 95% CI, 44-50 at 3 years; \( P < .001 \)).

**Mortality and relapse.** The Haplo-HCT group had a lower OS (48%; 95% CI, 42-54 vs 55%; 95% CI, 52-59 at 3 years; \( P = .03 \)) and a trend for higher NRM (19%; 95% CI, 15-24 vs 14%; 95% CI, 12-17 at 3 years; \( P = .06 \)) but similar relapse (\( P = .90 \)) and LFS (\( P = .11 \)). Center effect (tested for OS) was not significant (\( P = .08 \)).

### Table 1. (continued)

| Variable                                | Haplo (n = 336) | MSD (n = 869) | \( P \) |
|-----------------------------------------|-----------------|---------------|---------|
| Female-female                           | 65 (19)         | 187 (22)      |         |

**Cytogenetics**
- Favorable: 12 (4) vs 26 (3) \( P < .001 \)
- Intermediate: 170 (50) vs 560 (64) \( P = .10 \)
- Poor: monosomal karyotype: 33 (10) vs 76 (9) \( P = .82 \)
- Poor: other: 70 (21) vs 174 (20) \( P = .16 \)
- Not tested or missing: 51 (15) vs 33 (4) \( P = .001 \)

**MRD prior to HCT**
- Negative: 250 (74) vs 598 (62) \( P = .10 \)
- Positive: 66 (20) vs 192 (23) \( P < .001 \)
- Missing: 20 (6) vs 79 (9) \( P = .001 \)

**Conditioning intensity**
- MAC with TBI: 34 (10) vs 216 (24) \( P < .001 \)
- MAC without TBI: 83 (25) vs 396 (45) \( P = .90 \)
- RIC/nonmyeloablative: 219 (65) vs 250 (30) \( P = .03 \)
- Missing: 0 vs 7 (1) \( P = .001 \)

**Graft source**
- Bone marrow: 208 (62) vs 56 (7) \( P = .001 \)
- Peripheral blood: 128 (38) vs 813 (93) \( P = .001 \)

**GVHD prophylaxis**
- CNI + methotrexate ± others: 3 (<1) vs 622 (70) \( P = .001 \)
- CNI + mycophenolate mofetil ± others: 322 (96) vs 154 (19) \( P = .001 \)
- Others: 9 (3) vs 88 (11) \( P = .001 \)
- Missing: 2 (<1) vs 5 (<1) \( P = .001 \)

**Year of HCT**
- 2008-2010: 36 (11) vs 424 (49) \( P = .001 \)
- 2011-2015: 300 (89) vs 445 (51) \( P = .001 \)

**Median follow-up of survivors (range), mo**
- 35 (3-97) vs 60 (3-119) \( P = .001 \)

Unless otherwise noted, all data are n (%).

Haplo, haploidentical; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm.

*All Haplo-HCT patients received PT-Cy, whereas all MSD patients received a CNI.

**Engraftment.** Neutrophil and platelet engraftment rates were lower in the Haplo-HCT group (92%; 95% CI, 89-95 vs 99%; 95% CI, 98-99 for neutrophils at 1 month; \( P < .001 \) and 89%; 95% CI, 85-92 vs 97%; 95% CI, 96-98 for platelets at 100 days, \( P < .001 \)).

**Multivariable analysis**

**OS and LFS.** Haplo-HCT and MSD groups were not different with regard to OS (hazard ratio [HR], 1.15; 95% CI, 0.95-1.38; \( P = .15 \)) (Figure 1). Significant predictors of worse OS included older age (\( P = .02 \)), worse performance status (Karnofsky performance status < 90 vs 90+, \( P = .01 \)), MRD positivity before HCT (\( P = .005 \)), worse cytogenetic risk (\( P < .001 \)), secondary AML (\( P < .001 \)), and recipient male sex (\( P = .03 \)) (Table 3).
predictors of relapse were MRD positivity before HCT (Prelapse (HR, 0.88; 95% CI, 0.70-1.10; seronegative) (Table 3). worse cytogenetic risk (score (Table 2).

Univariate analysis of outcomes

| Outcomes                    | Haploidentical | MSD | P     |
|-----------------------------|----------------|-----|-------|
| Neutrophil engraftment at 1 mo | 92 (89-95)     | 99 (98-99) | <.001 |
| Platelet engraftment at 100 d | 89 (85-92)     | 97 (96-98) | <.001 |
| Grade II-IV acute GVHD       |                |     | .98   |
| 100 d                       | 31 (26-36)     | 26 (23-29) | .09   |
| 6 mo                        | 32 (27-37)     | 30 (27-33) | .64   |
| Grade III-IV acute GVHD      |                |     | .28   |
| 100 d                       | 10 (7-14)      | 10 (8-12) | .94   |
| 6 mo                        | 10 (7-14)      | 12 (10-14) | .54   |
| Chronic GVHD                |                |     | <.001 |
| 1 y                         | 22 (18-27)     | 48 (45-52) | <.001 |
| 3 y                         | 26 (21-31)     | 56 (53-60) | <.001 |
| Extensive chronic GVHD       |                |     | <.001 |
| 1 y                         | 15 (11-19)     | 41 (38-44) | <.001 |
| 3 y                         | 16 (12-20)     | 44 (41-50) | <.001 |
| Relapse                     |                |     | .88   |
| 1 y                         | 30 (25-35)     | 30 (27-34) | .92   |
| 3 y                         | 38 (33-44)     | 38 (34-41) | .90   |
| NRM                         |                |     | .06   |
| 1 y                         | 13 (10-17)     | 10 (8-12) | .12   |
| 3 y                         | 19 (15-24)     | 14 (12-17) | .06   |
| LFS                         |                |     | .23   |
| 1 y                         | 56 (51-62)     | 59 (56-63) | .34   |
| 3 y                         | 43 (37-48)     | 48 (45-51) | .11   |
| OS                          |                |     | .03   |
| 1 y                         | 67 (62-72)     | 70 (67-73) | .23   |
| 3 y                         | 48 (42-54)     | 55 (52-59) | .03   |

All data are % (95% CI).

However, the Haplo-HCT group had a lower rate of chronic GVHD (HR, 0.38; 95% CI, 0.30-0.48; P < .001) (Figure 1). Other factors significantly associated with an increased risk for chronic GVHD were using a female donor (P = .007 for male patient and P = .02 for female patient vs a male-to-male transplant) and MAC without TBI (compared with MAC with TBI, P = .05) (Table 3).

The interaction between MRD positivity and donor type did not influence any of the outcomes.

Subgroup analysis

Next, we performed multivariable subgroup analyses to evaluate whether the association between Haplo-HCT and less chronic GVHD is limited to MAC vs RIC or peripheral blood vs bone marrow. When the analysis was limited to the MAC subgroup, Haplo-HCT was associated with a lower risk for chronic GVHD (HR, 0.44; 95% CI, 0.31-0.61; P < .001) compared with MSD. A similar result was obtained with analysis limited to RIC cases (Haplo-HCT vs MSD: HR, 0.34; 95% CI, 0.25-0.48; P < .001). When the analysis was limited to peripheral blood cases, Haplo-HCT was associated with a lower risk for chronic GVHD compared with MSD (HR, 0.68; 95% CI, 0.50-0.91; P = .009). The association was even stronger when the analysis was limited to bone marrow grafts (HR, 0.22; 95% CI, 0.15-0.31; P < .001). These results indicate that the association between Haplo-HCT and less chronic GVHD is not limited to a specific conditioning intensity or graft source.

Causes of death

Overall, 170 deaths occurred in the Haplo-HCT group, and 425 occurred in the MSD group. The 3 most common causes of death were similar between the groups: relapse (58% vs 60%, respectively), GVHD (1% acute and 0.6% chronic vs 4% acute and 6% chronic, respectively), and infection (8% vs 10%, respectively).

Discussion

Our results from this large CIBMTR analysis of AML patients transplanted in CR1 indicate similar outcomes after current standard practices of PT-Cy–based Haplo-HCT vs MSD HCT, with the exception of less chronic GVHD after Haplo-HCT. The unique features of our study were its focus on patients with AML in CR1 and inclusion of MRD information. Because MRD was not uniformly tested or reported by CIBMTR centers, we created a logical definition of MRD using the available data. The balance between the groups using our MRD definition was important in the analysis of outcomes. Our subgroup analyses suggested that the reduced incidence of chronic GVHD in Haplo-HCT was not limited to a specific graft source or conditioning intensity.

The reduction in the incidence of chronic GVHD in our study was not associated with improved survival. Although prospective studies of Haplo-HCT vs MSD have not been performed, our finding is consistent with large randomized studies in other settings, such as matched donor transplant using peripheral blood vs bone marrow as a graft source.23 Late infections and secondary malignancies are among the causes of NRM that could offset a potential survival benefit of less chronic GVHD. However, data on these factors were not available in the present study. Similarly, reduced rates of chronic GVHD in the Haplo-HCT group in our study were not associated with increased relapse. Our analysis was strengthened by disease uniformity (AML in CR1) and balanced MRD status between the groups, 2 key factors in the analysis of relapse. A previous study
comparing Haplo-HCT and MSD in patients with acute leukemia showed consistent results. In contrast, a recent study comparing the outcomes of Haplo-HCT and MSD in patients with relapsed/refractory AML showed worse outcomes (LFS, OS, NRM, infections) after Haplo-HCT. Chronic GVHD and its complications are the primary determinants of long-term quality of life after allogeneic HCT, although this relationship has not been studied after Haplo-HCT. Future research should address whether reduced chronic GVHD after Haplo-HCT results in better quality of life.

In a large study comparing PT-Cy–based Haplo-HCT with MUD in patients with AML, the incidence of acute and chronic GVHD was lower after Haplo-HCT, with no survival difference. Our cohorts were not different with regard to the incidence of acute GVHD, likely because of less acute GVHD in MSD compared with MUD. However, chronic GVHD results were consistent between the 2 studies, with Haplo-HCT yielding the best results. Considering our negative subgroup analyses for graft source and conditioning intensity, the lower incidence of chronic GVHD after Haplo-HCT is likely due to PT-Cy. This finding may explain negative findings for chronic GVHD in a previous large study of Haplo-HCT vs MSD in
Table 3. Multivariable analysis of outcomes

| Covariates        | HR (95% CI) | P    |
|-------------------|-------------|------|
| **OS**            |             |      |
| Main effect       | .15         |      |
| MSD               | Reference   |      |
| Haplo-HCT         | 1.15 (0.95-1.38) |      |
| Age, y            | .02         |      |
| 18-54             | Reference   |      |
| 55+               | 1.23 (1.03-1.45) |      |
| Sex               | .03         |      |
| Male              | Reference   |      |
| Female            | 0.84 (0.71-0.99) |      |
| Karnofsky score   | .03         |      |
| 90+               | Reference   |      |
| <90               | 1.23 (1.04-1.45) | .01  |
| Missing           | 0.80 (0.44-1.47) | .47  |
| Cytogenetics      | <.001       |      |
| Favorable         | Reference   |      |
| Intermediate      | 1.29 (0.74-2.25) | .38  |
| Poor: monosomal karyotype | 2.51 (1.39-4.54) | .002 |
| Poor: other       | 1.89 (1.07-3.34) | .03  |
| Missing           | 1.78 (0.96-3.31) | .07  |
| MRD at HCT        | .009        |      |
| Negative          | Reference   |      |
| Positive          | 1.32 (1.09-1.61) | .005 |
| Missing           | 1.30 (0.97-1.73) | .07  |
| AML type          | <.001       |      |
| De novo           | Reference   |      |
| Secondary         | 1.38 (1.15-1.65) |      |
| **NRM**           |             |      |
| Main effect       | .16         |      |
| MSD               | Reference   |      |
| Haplo-HCT         | 1.26 (0.92-1.74) | <.001|
| Age, y            | .001        |      |
| 18-54             | Reference   |      |
| 55+               | 1.97 (1.43-2.70) |      |
| Sex               | .01         |      |
| Male              | Reference   |      |
| Female            | 0.69 (0.52-0.92) |      |
| HCT-CI            | .005        |      |
| 0                 | Reference   |      |
| 1                 | 1.36 (0.86-2.17) | .19  |
| 2                 | 1.02 (0.61-1.73) | .93  |
| 3+                | 1.88 (1.31-2.71) | <.001 |
| Missing           | 1.42 (0.67-3.05) | .36  |
| Conditioning      | .06         |      |
| MAC-TBI           | Reference   |      |
| MAC without TBI   | 0.67 (0.47-0.98) | .04  |
| RIC               | 0.57 (0.38-0.86) | .008 |
| Missing           | 0.56 (0.08-4.14) | .57  |

Table 3. (continued)

| Covariates        | HR (95% CI) | P    |
|-------------------|-------------|------|
| **Relapse**       |             |      |
| Main effect       | .27         |      |
| MSD               | Reference   |      |
| Haplo-HCT         | 0.88 (0.70-1.10) |      |
| Cytogenetics      | <.001       |      |
| Favorable         | Reference   |      |
| Intermediate      | 1.26 (0.69-2.32) | .45  |
| Poor: monosomal karyotype | 2.48 (1.30-4.72) | .006 |
| Poor: other       | 2.01 (1.08-3.74) | .03  |
| Missing           | 1.76 (0.88-3.50) | .11  |
| MRD at HCT        | .003        |      |
| Negative          | Reference   |      |
| Positive          | 1.45 (1.17-1.80) | <.001|
| Missing           | 1.19 (0.84-1.67) | .33  |
| Conditioning      | .004        |      |
| MAC-TBI           | Reference   |      |
| MAC without TBI   | 1.01 (0.78-1.30) | .95  |
| RIC               | 1.43 (1.10-1.85) | .008 |
| Missing           | 0.35 (0.05-2.50) | .29  |
| **aGVHD II-IV**   |             |      |
| Main effect       | .95         |      |

aGVHD, acute GVHD; CMV, cytomegalovirus; D/R, donor/recipient; F, female; M, male; TBI, total body irradiation.
patients with intermediate- or poor-risk AML in CR1, because more than 25% of Haplo-HCT patients in that study did not receive PT-Cy. Most of our MSD recipients received peripheral blood stem cells, and nearly half developed chronic GVHD at 1 year. The associations between donor type and outcome in our study did not depend on MRD status before HCT. To our knowledge, only 1 previous study found differential outcomes between donor types depending on MRD status. In that study, patients with AML or myelodysplastic syndrome received a myeloablative cord blood or MUD transplant. The use of cord blood resulted in less relapse and higher OS compared with an MSD using peripheral blood and CNI-based GVHD prophylaxis. In this study, we did not consider viral reactivations and hemorrhagic cystitis, which could differ between the 2 groups.

In conclusion, a haploidentical relative is a viable alternative to an MSD in AML patients in CR1. The longer interval between diagnosis and transplant in our Haplo-HCT recipients suggests that, in some cases, centers might have spent time looking for unrelated donors before turning to haploidentical donors. Our results can help to prevent this delay in choosing a suitable donor. Choosing a haploidentical donor over a matched sibling may be necessary when stem cell collection from a matched sibling is considered risky because of comorbidities, and our results provide support for this approach. In addition, more than one fifth of our Haplo-HCT patients were African American, supporting the feasibility of using this donor type in ethnic minorities. Finally, a future study comparing Haplo-HCT with MSD, using the same graft source and PT-Cy prophylaxis, would be mechanistically informative about whether PT-Cy negates the effect of HLA disparity on outcomes.

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