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Comparable Outcomes after Hematopoietic Stem Cell Transplantation from Mother Donors and Matched Unrelated Donors in Patients with Hematopoietic Malignancies

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A B S T R A C T

Haploidentical transplantations have achieved comparable survival as HLA fully matched unrelated donors (URDs). When choosing the best donor for HLA haploidentical transplantations, most institutions prioritize using young male donors over mother donors. In a retrospective study we compared outcomes in mother donor and URD transplantations. We found that both 2-year overall survival and 2-year leukemia-free survival were comparable between the mother donor group and URD group (74.8% versus 72.9%, $P = .937$, and 71.7% versus 67.0%, $P = .580$, respectively). Higher incidences of grades II to IV acute graft-versus-host disease (GVHD) and chronic GVHD were observed in the mother donor group than in the URD group (43.5% versus 14.0%, $P = .001$, and 62.2% versus 38.7%, $P = .007$, respectively). The 2-year cumulative incidences of relapse were significantly decreased in the mother donor group (7.6% versus 20.9%, $P = .036$). These findings suggest mother donor transplantations could achieve comparable survival with URD transplantations and exhibited decreased rates of relapse but increased rates of GVHD, indicating that mother donors would be a suitable choice for patients without an identical sibling donor.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) is a potentially curative treatment for hematologic malignancies. To date, most studies consider matched unrelated donors (URDs) as the preferential choice of HSCT donors when there are no HLA-identical sibling donors (ISDs). Progress in HLA typing, graft-versus-host disease (GVHD), prophylaxis and patient care has led to equivalent outcomes for URD to ISD transplantations, although shortages in donors still exist [1–4]. Development of haploidentical donor (HID) transplantation has enabled identification of a suitable donor for almost all patients. Previous research has suggested equivalent survival in the settings of unmanipulated HID versus URD transplantations in a variety of hematopoietic malignancies, both in the post-transplant cyclophosphamide modality and in the Beijing Protocol [5–10]. In the study from Xiaojun et al. [5] using the Beijing Protocol, the 2-year incidence of relapse for standard-risk patients was lower in the HID group compared with that of the URD group, indicating a potential for greater graft-versus-leukemia (GVL) effect of HIDs. Similar results were reported by Luo et al. [6], suggesting application of HIDs was comparable with URDs, especially in terms of preventing relapses.

Although observational studies appear to show similar results for HIDs versus URDs, there are still questions to answer regarding selecting the most appropriate donor for a given patient when both HIDs and matched URDs are available. It is accepted that non-HLA factors, such as donor age and gender, could affect outcomes of HSCT in both HIDs and URDs, meaning there are better and worse donors within each. Comparing outcomes from "the worst" donor within HIDs and "the best" donor within URDs would help to answer the above question. Under the Beijing Protocol, previous studies suggested that young male donors were associated with reduced transplant-related mortality (TRM) and improved survival [11–13]. When compared with paternal donors, maternal donors demonstrated increased risks of TRM and acute GVHD, thus resulting in inferior survival. In haploidentical SCT with a post-transplant cyclophosphamide regimen, influences of donor age on outcomes were controversial, but parental

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donors were associated with increased risks of graft failure and relapse and inferior overall survival (OS) [14–16]. Therefore, in unmanipulated HID transplant settings, offspring and sibling donors were prioritized over parental donors. Under the Beijing Protocol, maternal donors should be avoided based on current studies.

In this present study we compared transplantation outcomes of maternal donors, which were considered as "the last choice" in HIDs, with outcomes of URDs under the Beijing Protocol. Besides answering the question on donor selection between HIDs and URDs, this study is practically significant because of current shortage of URDs in the Chinese donor registry. Especially because of the 1 family, 1 child policy in China, most young patients have no sibling donors. In some cases their fathers are not suitable for donation either. Thus, it remains unanswered whether, in the absence of a sibling or paternal donor, maternal donors should be used or if waiting for an URD is best. By using data on the Beijing Protocol, our study provides further information on donor selection between HIDs and URDs in HSCT.

METHODS

Patients and Donors

Between June 2012 to June 2015, 92 patients with hematopoietic malignances received transplantations from mother donors and 43 patients received transplantations from URDs at Peking University Institute of Hematology. The study procedure was approved by the ethics committee of Peking University People's Hospital. Written informed consent was given by all enrolled patients.

URDs were chosen from the Chinese donor registry program. Prioritization in choosing an URD in our institute was as follows: 10/10 HLA matching donors were prioritized over 9/10 or 8/10 matches, younger and male donors were preferred, and ABO matched donors were preferred. Serum cytomegalovirus status was not included in the criteria when choosing URDs because of the very high positivity of cytomegalovirus IgG in the Chinese population.

Transplantation Regimens

For patients receiving HSCT from mother donors, the pretransplant conditioning regimen consisted of cytarabine 4 g/m^2 per day at days −10 and −9, busulfan 3.2 mg/kg a day i.v. at days −8 to −6, cyclophosphamide 1.8 g/m^2 a day at days −5 to −4, and rabbit antithymocyte globulin 2.5 mg/kg a day at days −5 to −2. Patients who received conditioning with total body irradiation were irradiated with 770 cGy at day −6, together with the same cyclophosphamide and antithymocyte globulin doses as described above. Grafts from both bone marrow and peripheral blood were harvested and infused following protocols described by our institute previously [17,18].

The conditioning protocol for URD transplants was identical to that of the mother donor group, except a reduced dose of cytarabine at 2 g/m^2 a day was used at days −10 and −9. Patients received grafts from peripheral blood of URDs. For GVHD prophylaxis patients received cyclosporine, mycophenolate mofetil, and methotrexate. Cyclosporine (2.5 mg/kg a day i.v.) was initiated from day 29 and switched to oral administration (3 to 5 mg/kg a day) after bowel function normalized. Blood cyclosporine concentration was maintained at 150 to 250 ng/mL and was then gradually reduced in patients without GVHD on day +180. Mycophenolate mofetil at .5 g p.o. was administered every 12 hours from days 29 to 30. The dose was then tapered to half and discontinued at day 60. Methotrexate 15 mg/m2 was administered i.v. at day 1 and was reduced to 10 mg/m2 at days 3, 5, and 11.

Definitions

Disease risk index of patients was defined according to research from Armand et al. [19]. Engraftment, graft failure, TRM, leukemia-free survival (LFS), and overall survival (OS) were defined as previously described [17,20]. Relapse was defined on the basis of bone marrow histology with more than 5% blasts. Acute GVHD was defined and graded according to published studies [21,22]. Chronic GVHD was defined and graded based on the National Institutes of Health criteria [23].

Donor lymphocyte infusions

Donor lymphocyte infusions (DLIs) were performed as described [24,25]. In the present study patients received DLIs for disease relapse indicated by bone marrow histology, positivity of minimal residual disease, and graft failure.

Statistics

For patient characteristics, continuous variables were compared using the Mann-Whitney U test; categorical variables were compared using the chi-square or Fisher's exact test. Cumulative incidences of GVHD, TRM, and relapse were calculated in a competing risk setting, with death as the competing event for relapse, relapse as the competing event for TRM, and death, DLI, and relapse as the competing risks for GVHD. Probabilities of OS and LFS were estimated by Kaplan-Meier curves. All variables in Table 1were included in a univariate analysis. Only variables with $P < .1$ were included in further multivariate analysis. $P < .05$ was considered as statically significant, unless explicitly described. All analyses were conducted using SPSS (version 23.0; Chicago, IL) and R software (Bell Labs, New Providence, NJ).

RESULTS

Patient Characteristics

Characteristics of patients, donors, and grafts within each group are summarized in Table 1. Some features differed between groups. In the mother donor group all patients received HSCs from mothers, 74 with 3 mismatched HLA loci (3/6 matches) and 18 with 2 (4/6 matches) in HLA-A, -B and -DR loci. In the URD group 34 patients received HLA-A, -B, -C, -DR, and -DQ 10/10 matched HSCs from URDs, and 9 patients received HSCs that had a single HLA locus mismatch from donors (9/10 matches). The median age of recipients was 21.5 years (range, 5 to 48) in the mother donor group and 29 years (range, 5 to 56) in the URD group ($P = .001$). The median age of donors also differed between the 2 groups, with 44 years (range, 28 to 67) for the mother donor group and 29 years (range, 18 to 45) for the URD group ($P = .001$). The number of infused CD34$^+$ cells was higher in the URD group than in the mother donor group ($P = .001$). Other characteristics, including gender, primary diseases, disease risk index, and status before transplantation, were comparable between the 2 groups (Table 1).

The last follow up date was November 1, 2017. The median follow-up time was 27 months (range, .5 to 60) for the mother donor group and 24 months (range, 1.5 to 58) for the URD group.

Hematopoietic Recovery

In the mother donor group all patients achieved neutrophil recovery except for 1 patient who died at day 7 post-transplantation. In the URD group 1 patient failed to achieve neutrophil or platelet recovery and died at day 229. Among engrafted patients neutrophil recovery occurred at a median of 13 days (range, 10 to 21) and 11 days (range, 9 to 27) in the mother donor group and URD group, respectively ($P = .280$). Four patients in the mother donor group and 5 patients in the URD group experienced failure for platelet recovery. For engrafted patients platelet recovery occurred at a median of 16 days (range, 8 to 115) in the mother donor group and 12 days (range, 8 to 149) in the URD group ($P = .150$). The 100-day cumulative incidence of platelet recovery was 98.9% in the mother donor group, which was slightly higher than that in the URD group (97.4%, $P = .011$).

Acute and Chronic GVHD

With death as a competing risk, the 100-day cumulative incidence of grades II to IV acute GVHD was significantly higher in the mother donor group (43.5%) compared with that in the URD group (14.0%, $P = .001$) (Figure 1A), whereas incidences of grades III to IV acute GVHD were similar between groups (mother donor group, 12%; URD group, 7%; $P = .374$) (Figure 1B). The 2-year cumulative incidence of chronic GVHD was 62.2% in the mother donor group and 38.7% in the URD group ($P = .007$) (Figure 1C). Moderate to severe GVHD was also more frequently seen in the mother donor group (40.5%;

Table 1
Patients Characteristics

Characteristics	URD (n = 43)	Mother Donor (n = 92)	*P*
Median recipient age, yr (range)	29.0 (5-56)	21.5 (5-48)	.001
Male sex	19 (44.2)	42 (45.7)	.719
Median donor age, yr (range)	29 (18-45)	44 (28-67)	.001
Disease			
AML	18 (41.9)	39 (42.4)	.088
ALL	13 (30.2)	44 (47.8)	
MDS	8 (18.6)	5 (5.4)	
CML	2 (4.7)	4 (4.3)	
Other	2 (4.7)	2 (2.2)	
Disease status before HSCT			
CR1	39 (90.7)	76 (82.6)	.166
CR > 1	4 (9.3)	16 (17.4)	
Disease risk index			
Low	3 (7.0)	16 (17.4)	.238
Intermediate	34 (79.1)	67 (72.8)	
High	6 (14.0)	9 (9.8)	
Conditioning regimen			
Chemotherapy based	43 (100)	84 (91.3)	.109
TBI based*	0 (0)	8 (8.7)	
HLA disparity			
0	34 (79.1)	0 (0)	
1	9 (20.9)	0 (0)	
2	0 (0)	18 (19.6)	
3	0 (0)	74 (80.4)	
Donor–recipient sex-matched grafts			
Male–male	17 (39.5)	0 (0)	
Male–female	22 (51.2)	0 (0)	
Female–male	2 (4.7)	42 (45.7)	
Female–female	2 (4.7)	50 (54.3)	
ABO matched grafts			
Matched or minor mismatch	28 (65.1)	61 (66.3)	.892
Major or bidirectional mismatch	15 (34.9)	31 (33.7)	
Cell compositions in allografts			
Median infused nuclear cells, 10^8/kg (range)	7.58 (3.00-16.99)	7.77 (3.36-20.28)	.270
Median infused $CD34^+$ cells, 10^6/kg (range)	4.00 (.70-11.67)	2.34 (.71-10.47)	.001
Median infused $CD3^+$ cells, 10^8/kg (range)	1.98 (.89-5.67)	1.32 (.29-2.79)	.034
DLI after transplant	7 (16.3)	12 (13.0)	.605

Values are n (%) unless otherwise defined. AML indicates acute myeloid leukemia; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndrome; CML, chronic myeloid leukemia; CR, complete remission; CR1, first CR; TBI, total body irradiation.
* TBI was performed before HSCT for the reason of extramedullary disease.

URD group, 11.5%; $P = .001$) (Figure 1D). Multivariate analysis indicated increased rates of acute GVHD were associated with mother donor transplant (hazard ratio [HR], 2.049; $P = .017$), and chronic GVHD was related to lower doses of CD34 cells infused (HR, 1.834; $P = .035$) and female-to-male donations (HR, 1.733; $P = .047$).

Relapse and TRM

At last follow-up on November 1, 2017, 9 patients in the mother donor group and 10 patients in the URD group relapsed. All relapses occurred in the first 24 months after HSCT in the URD group, whereas 1 patient developed relapse at day 1179 in the mother donor group. As shown in Figure 2A, the 2-year cumulative incidences of relapse were significantly lower in the mother donor group (7.6%) than in the URD group (20.9%; $P = .036$). In the mother donor group 2 patients experienced relapses in the central nervous system, whereas 7 experienced bone marrow relapses. In the URD group 2 patients experienced extramedullary relapses and 8 experienced bone marrow relapse. In the mother donor group 8 patients received DLIs plus chemotherapy as treatment of hematologic relapse and 4 patients received preemptive DLIs as intervention for positive minimal residual disease. In the URD group 6 patients received DLIs for hematologic relapse and 1 patient received DLI for positive minimal residual disease. Multivariate analysis revealed that relapse was associated with both donor types and disease status before HSCT, as shown in Table 3.

Table 2
Primary Causes of Death

	Mother Donor	URD
Total	21	11
Infection	14 (66.7%)	6 (54.5%)
Relapse	4 (19.0%)	3 (27.2%)
GVHD	2 (9.5%)	1 (9.1%)
Veno-occlusive disease	1 (4.76%)	1 (9.1%)

The 2-year cumulative incidences of TRM between the 2 groups were not statistically different (mother donor group, 21.1%; URD group, 11.6%; $P = .173$) (Figure 2B). Causes of TRM included infections (mother donor group, 14 cases; URD group, 6 cases), severe GVHD (mother donor group, 2 cases; URD group, 1 case), and hepatic failure (mother donor group, 1 case; URD group, 1 case) (Figure 2), (Table 2). A lower dose of infused CD34 cells was the only risk factor for increased TRM in our multivariate analysis (HR, 4.856; $P = .004$).

OS and LFS

The 2-year probability of OS was not significantly different between the 2 groups (mother-donor group, 74.8%; URD

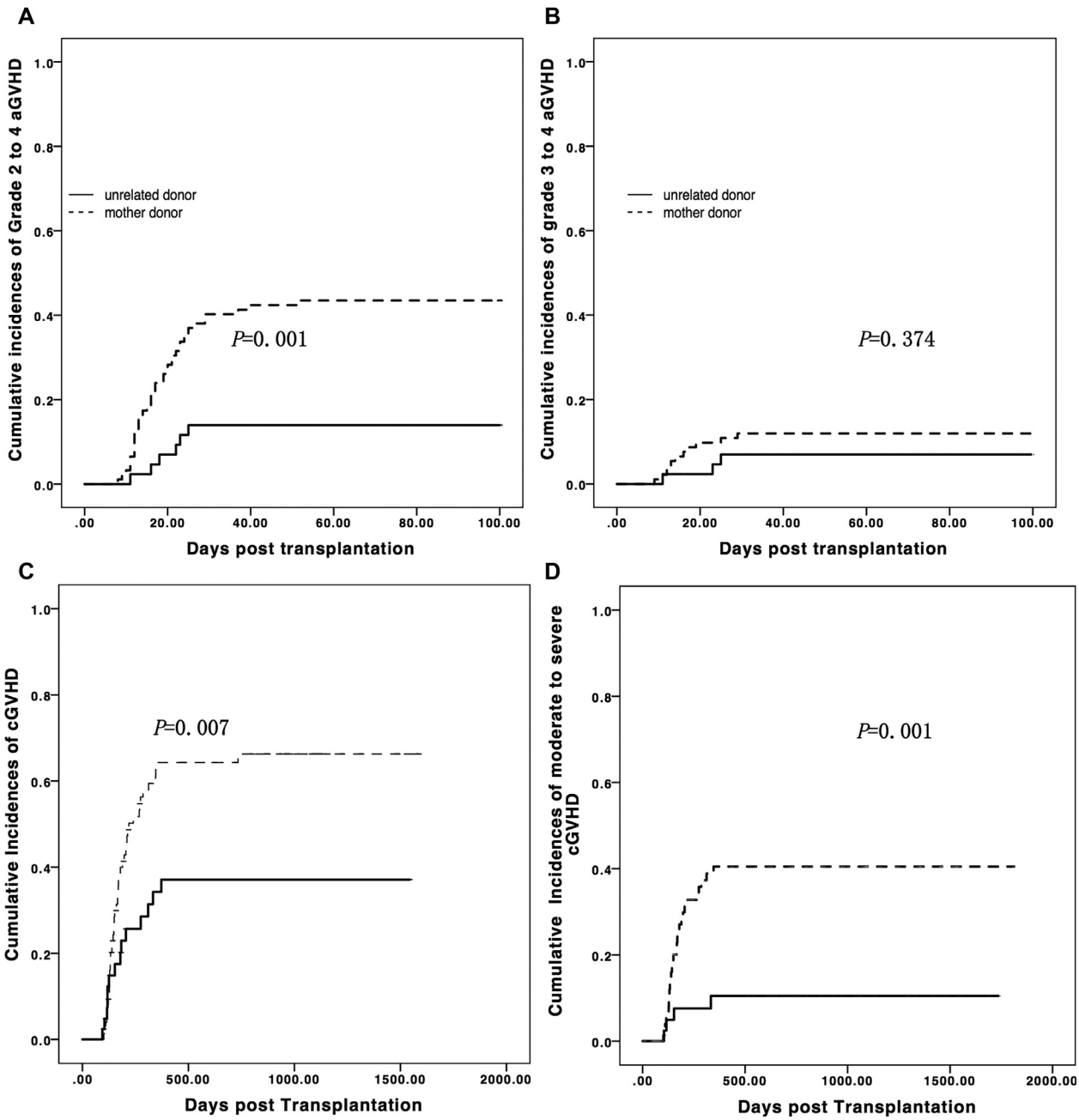

Figure 1. Incidences of acute and chronic GVHD. (A) Cumulative incidences of grades II to IV acute GVHD. (B) Cumulative incidences of grades III to IV acute GVHD. (C) Cumulative incidences of chronic GVHD. (D) Cumulative incidences of moderate to severe chronic GVHD.

group, 72.9%; $P = .937$) (Figure 2C). Inferior OS was associated with a disease status of more than first complete remission or no response before HSCT (HR, 2.809; $P = .006$) and an absence of chronic GVHD (HR, 2.309; $P = .020$) in the univariate analysis; these factors remained significant in the multivariate analysis. The 2-year probabilities of LFS were also comparable between groups (mother donor group, 71.7%; URD group, 67.0%; $P = .580$) (Figure 2D). Disease status (HR, 2.960; $P = .002$) and chronic GHVD (HR, 2.418; $P = .007$) proved to be risk factors for LFS in the multivariate analysis.

We further compared outcomes in female and male recipients in the mother donor group with URD transplants separately. The 2-year probabilities of OS were 82.6% in female recipients and 68.6% in male recipients of the mother donor group, which were of no statistical significance compared with URD transplant ($P = .365$ and $P = .579$, respectively). Two-year LFS was 78% in female recipients and 66.7% in male recipients, which was also similar to URD transplant ($P = .259$ and $P = .936$, respectively). Comparable incidences of TRM were observed when comparing female and male recipients with URD transplantations ($P = .706$ and $P = .065$, respectively), although male recipients exhibited a trend of higher TRM. Reduced incidences of relapse were found in both female and male recipients compared with that of the URD transplant ($P = .040$ and $P = .026$, respectively).

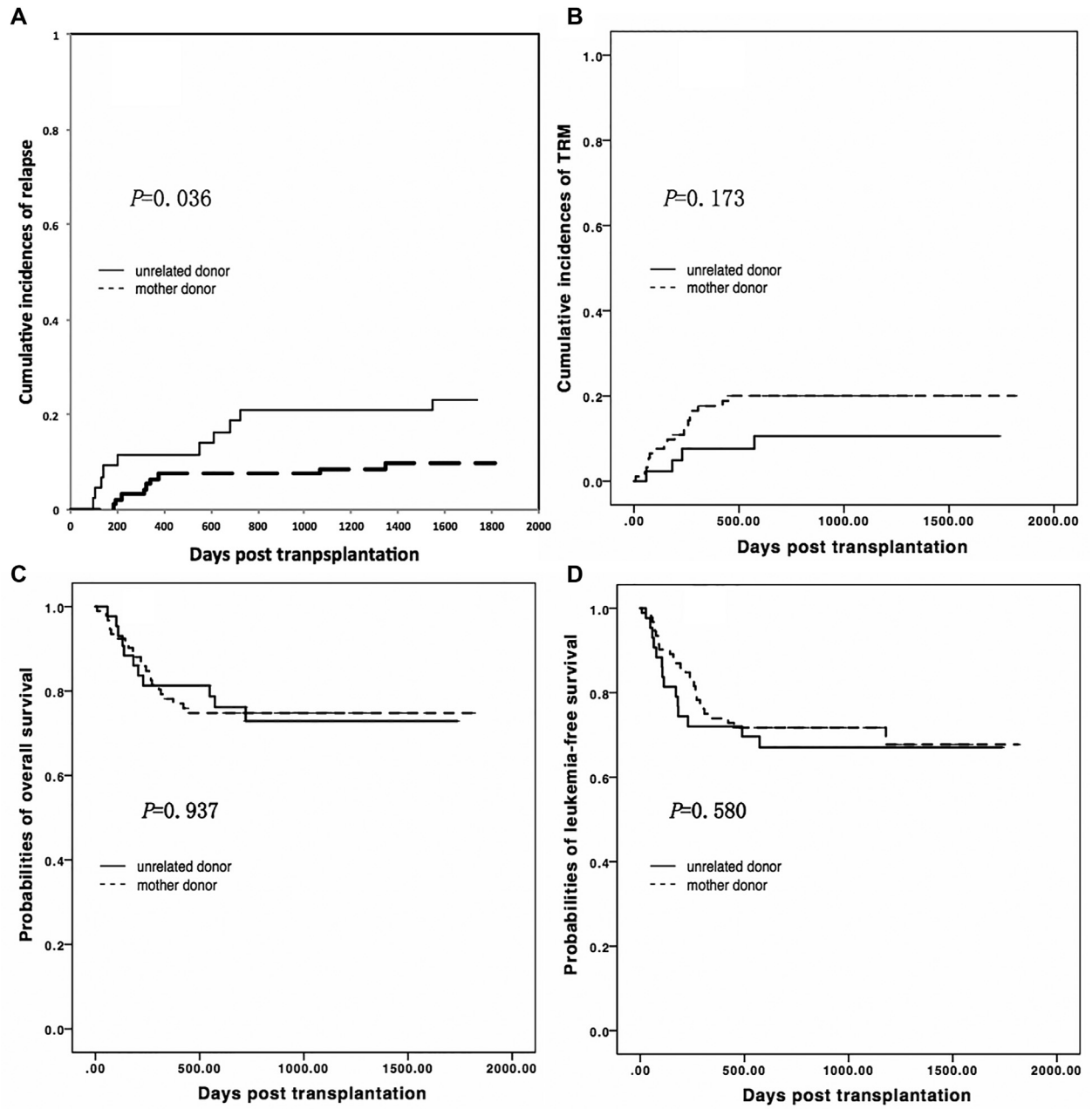

Figure 2. Relapse, TRM, OS, and LFS. (A) Cumulative incidences of relapse. (B) Cumulative incidences of TRM. (C) Probabilities of OS. (D) Probabilities of LFS.

DISCUSSION

Given the increasing interest in HID transplantation, many publications have compared outcomes of HIDs with other donor sources. Current data suggest equivalent survival after HIDs and URDs [5–10]. However, previous studies usually consider the 2 donor sources each as a homogenous group when making the comparison, although there are actually subgroups within each. To further determine donor prioritization, we compared the "worst donor" in HID with the "best donor" in URD in HSCT using the Beijing Protocol. In HIDs published data usually consider young male donors as preferred and mother donors as avoided [12,13,26]. In URDs donor age and degree of HLA match were related to transplant outcomes [27,28]. Thus, the ideal condition was to compare mother donors in HIDs with young and 10/10 matched donors in URDs. However, the relatively small sample number in our URD group has limited its subgrouping, despite that most URDs in our study were younger than 35 years (31/43) and 10/10 matched with their recipients (34/43). Therefore, we retrospectively collected outcomes of HID patients transplanted with mother donors and all patients transplanted with URDs from June 2012 to June 2015 to add information on donor selection between HIDs and URDs.

One of the major concerns when choosing maternal donors is the increased possibility of GVHD. Our data did suggest higher incidences of grades II to IV acute GVHD in the mother donor cohort, although grades III to IV acute GVHD occurred at comparable rates between 2 groups, which was consistent with studies from Tamaki et al. [29] in T cell–deplete HIDs. The mother donor group also showed relatively higher incidences of chronic GVHD and moderate to severe chronic GVHD. Our regression analysis did find mother donors as a risk

Table 3
Univariate and Multivariate Analyses for Transplant Outcomes

	Univariate Analysis			Multivariate Analysis		
Outcomes	HR	95% CI	*P*	HR	95% CI	*P*
OS						
Disease status (CR1 vs. others)	.356	.170-.746	.006	.296	.139-.629	.002
Chronic GVHD (no vs. yes)	2.309	1.142-4.669	.02	2.677	1.309-5.476	.007
LFS						
Disease status (CR1 vs. others)	.370	.185-.741	.005	.338	.161-.652	.002
Chronic GVHD (no vs. yes)	2.178	1.152-4.119	.017	2.418	1.272-4.599	.007
TRM						
Infused CD34 cells (< median vs. ≥ median)	4.995	1.689-14.766	.004	4.856	1.641-14.369	.004
Donor–recipient sex (others vs. female donors to male recipients)	.471	.204-1.087	.078			
Relapse						
Donor type (URD vs. mother)	2.533	1.029-6.235	.043	2.524	1.189-6.281	.035
Disease status (CR1 vs. others)	.239	.094-.608	.003	.201	.077-.521	.001
Risk index (standard risk vs. others)	.256	.092-.712	.009			
Acute GVHD (no vs. yes)	2.370	.961-5.850	.061			
Acute GVHD						
Donor type (URD vs. mother)	.386	.232-.641	<.001	.437	.258-.761	.003
Donor–recipient sex (others vs. female donors to male recipients)	.592	.387-.905	.016			
Chronic GVHD						
Donor type (URD vs. mother)	.439	.243-.792	.006			
Infused CD34 cells (< median vs. ≥ median)	2.084	1.257-3.454	.004	1.754	1.032-2.985	.038
Donor–recipient sex (others vs. female donors to male recipients)	.561	.343-.917	.021	.612	.380-.988	.045

CI indicates confidence interval. All factors with $P < .1$ were included in the multivariate analysis.

factor for acute GVHD. However, it is worth noting that some unbalanced baseline factors, including gender and age of donors and infused CD34 cell dose, may also influence risks of GVHD. In the present study most URDs were male (39/43, 90.7%), whereas all donors in the mother donor group were certainly female. Previous study has indicated that male recipients of female grafts exhibited increased risks of GVHD, as we observed in our study [30]. Furthermore, studies from Wang et al. [12] and Kollman et al. [31] showed donors older than 30 years were associated with increased GVHD. The median donor age in the mother donor group was 44 years, which may be another reason for more GVHD in this group. Additionally, less CD34-positive HSCs were infused into patients in the mother donor group, which may also account for increased chronic GVHD. These data supported findings of our multivariate analysis suggesting that donor type may not be, or at least not the only explanation, for increased GVHD in this study.

Relapse is the most common cause of treatment failure after HSCT. In this study we observed less relapses in the mother donor group, even though there were fewer acute lymphoblastic leukemia patients in first complete remission in this group, indicating a superior GVL effect. This effect may be partially attributed to increased chronic GVHD, which was supported by studies from Baron et al. [32] and Signori et al. [33]. In addition, more grade II acute GVHD was observed in the mother donor group than in the URD group, which may also account for less relapse in the mother donor group based on a study from McCurdy et al. [34]. Female donors to male recipients may be another reason for less relapses in the mother donor group, as previously indicated by Randolph et al. [30]. Thus, besides sources of HSCs, reduced relapse in the mother donor group may also be associated with female to male transplantations and GVHD. Because this study was retrospective, it was hard to distinguish these interfering factors from the donor source factor on which we were focusing. However, in that there were nonrelapsed female patients who did not develop GVHD in the mother donor group, these factors could not explain all GVL effects in the mother donor group. This was further confirmed in our multivariate analysis, in which only donor type and disease status remained meaningful, indicating HSCs from mother donors may exhibit GVL effect.

Despite higher incidences of acute and chronic GVHD, TRM was not increased in the mother donor group. Meanwhile, less relapses were observed in the mother donor group. Thus, equivalent OS and LFS to URD recipients were achieved in the present study. This was also confirmed in our multivariate analysis for OS and LFS, in which no correlations between donor types and OS/LFS were found. Factors affecting OS included disease status and chronic GVHD, which was consistent with previous studies [35–37]. From our analysis, lower OS was associated with the absence of chronic GVHD (Table 3). Incidences of chronic GVHD were lower in the URD group (37.1%), which may partially contribute to the comparable OS observed in the 2 groups. There is indeed a possibility that with increased numbers of URD transplants, higher chronic GVHD may be observed. However, in published studies with more URD cases from Xiaojun et al. [5] (n = 78) and Luo et al. [6] (n = 116) using the Beijing Protocol, chronic GVHD incidences were 40% and 41.7%, respectively, which were slightly but not hugely higher than that in our study. Nevertheless, we did keep in mind that case numbers in the URD group were relatively low, and further studies with more URDs are required.

Therefore, even though our previous study suggested mother donor HSC recipients exhibited inferior survival among all family relationships in HIDs, considering the comparable survival between mother donors and URDs, mother donors may provide treatment options in the absence of other suitable donors, especially for high-risk malignancies. In addition, time from diagnosis to transplant was a potential risk factor for prognosis, because repeated consolidation chemotherapy might lead to cumulative organ damage [38]. Availability of mother donors avoided the long waiting period in finding matched URDs. Therefore, although cases were limited, we intend to recommend with caution that for standard-risk

patients, URDs might be chosen because of the low incidences of GVHD, and for high-risk patients mother donors might be a better choice to prevent relapse given ready availability and increased GVL when using the Beijing Protocol.

The major limitation of this study was the relatively small sample size, especially in the URD group because of shortages of available donors in the Chinese URD registry and differences in races and ethnicity from other donor registries. This prevented us from performing further analysis on "the best" URD transplantations with young and HLA 10/10 matched donors as previous data suggested [28]. However, from our preliminary results (data not shown), comparable OS and LFS were observed between the HLA 10/10 matched URDs and mother donors (OS, 75.4% versus 74.8% [$P = .802$]; LFS, 68.2% versus 71.7% [$P = .673$]). Furthermore, younger URDs (no more than median age) exhibited a trend of improved OS to older URDs (more than median age) but comparable with that of the mother donor group (82% versus 74.8%, $P = .321$). Also, because of the retrospective nature of this study some unbalanced variables, such as recipient age, existed in the 2 groups. To minimize this we performed a matched pair analysis for patients from the 2 cohorts according to recipient age ($P = .121$), gender ($P = .212$), and disease status ($P = .822$). Comparable OS and LFS were observed in the matched pair analysis as shown in Supplementary Figure 1.

Another limitation of our study was the relatively low recipient age, which may limit the applicability of our results to elderly recipients. Thus, studies including more elderly recipients should be carried out in the future. Despite these limitations, our study made up the gap for donor selection between the specified HIDs (ie, the maternal donors) and URDs.

In conclusion, our results indicated that mother donor transplantations could achieve comparable OS and LFS with URDs under the Beijing Protocol. This study shed light on donor selection by using 1 modality (the Beijing Protocol) to answer the universal question of HIDs versus URDs. Further prospective studies from multicenters using various transplantation modalities with larger number of cases and prolonged follow-up are recommended to validate our findings.

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SUPPLEMENTARY MATERIALS

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2019.01.030.

REFERENCES

1. Yakoubagha I, Mesnil F, Kuentz M, et al. Allogeneic marrow stem-cell transplantation from human leukocyte antigen-identical siblings versus human leukocyte antigen-allelic-matched unrelated donors (10/10) in patients with standard-risk hematologic malignancy: a prospective study from the French S. *J Clin Oncol*. 2006;24:5695–5702.
2. Schetelig J, Bornhauser M, Schmid C, et al. Matched unrelated or matched sibling donors result in comparable survival after allogeneic stem-cell transplantation in elderly patients with acute myeloid leukemia: a report from the cooperative German Transplant Study Group. *J Clin Oncol*. 2008;26:5183–5191.
3. Gupta V, Tallman MS, He W, et al. Comparable survival after HLA-well-matched unrelated or matched sibling donor transplantation for acute myeloid leukemia in first remission with unfavorable cytogenetics at diagnosis. *Blood*. 2010;116:1839–1848.
4. Karanes C, Nelson GO, Chitphakdithai P, et al. Twenty years of unrelated donor hematopoietic cell transplantation for adult recipients facilitated by the National Marrow Donor Program. *Biol Blood Marrow Transplant*. 2008;14(9 Suppl):8.
5. Huang X, Xu L, Liu K, et al. Partially matched related donor transplantation can achieve outcomes comparable with unrelated donor transplantation for patients with hematologic malignancies. *Clin Cancer Res*. 2009;15:4777.
6. Luo Y, Xiao H, Lai X, et al. T-cell-replete haploidentical HSCT with low-dose anti-T-lymphocyte globulin compared with matched sibling HSCT and unrelated HSCT. *Blood*. 2014;124:2735–2743.
7. Bashey ZA, Zhang X, Brown S, et al. Comparison of outcomes following transplantation with T-replete HLA-haploidentical donors using post-transplant cyclophosphamide to matched related and unrelated donors for patients with AML and MDS aged 60 years or olde. *Bone Marrow Transplantation*. 2018;53:756–763.
8. Gu Z, Wang L, Yuan L, et al. Similar outcomes after haploidentical transplantation with post-transplant cyclophosphamide versus HLA-matched transplantation: a meta-analysis of case-control studies. *Oncotarget*. 2011;8:63574–63586.
9. Ciurea SO, Zhang MJ, Bacigalupo AA, et al. Haploidentical transplant with posttransplant cyclophosphamide vs matched unrelated donor transplant for acute myeloid leukemia. *Blood*. 2015;126:1033.
10. McCurdy SR, Kasamon YL, Kanakry CG, et al. Comparable composite endpoints after HLA-matched and HLA-haploidentical transplantation with post-transplantation cyclophosphamide. *Haematologica*. 2017;102:391.
11. Xu L, Chen H, Chen J, et al. The consensus on indications, conditioning regimen, and donor selection of allogeneic hematopoietic cell transplantation for hematological diseases in China-recommendations from the Chinese Society of Hematology. *J Hematol Oncol*. 2018;11:33.
12. Wang Y, Chang YJ, Xu LP, et al. Who is the best donor for a related HLA haplotype-mismatched transplant? *Blood*. 2014;124:843.
13. Chang YJ, Luznik L, Fuchs EJ, Huang XJ. How do we choose the best donor for T-cell-replete, HLA-haploidentical transplantation? *J Hematol Oncol*. 2016;9:35.
14. Canaani J, Savani BN, Labopin M, et al. Donor age determines outcome in acute leukemia patients over 40 undergoing haploidentical hematopoietic cell transplantation. *Am J Hematol*. 2017;93:246.
15. McCurdy SR, Zhang MJ, St AM, et al. Effect of donor characteristics on haploidentical transplantation with posttransplantation cyclophosphamide. *Blood Advances*. 2018;2:299–307.
16. Solomon SR, Aubrey MT, Zhang X, et al. Selecting the best donor for haploidentical transplant: impact of HLA, killer cell immunoglobulin-like receptor genotyping, and other clinical variables. *Biol Blood Marrow Transplant*. 2018;24:789–798.
17. Wang Y, Fu HX, Liu DH, et al. Influence of two different doses of antithymocyte globulin in patients with standard-risk disease following haploidentical transplantation: a randomized trial. *Bone Marrow Transplant*. 2014;49:426.
18. Huang XJ, Liu DH, Liu KY, et al. Haploidentical hematopoietic stem cell transplantation without in vitro T-cell depletion for the treatment of hematological malignancies. *Bone Marrow Transplant*. 2006;38:291.
19. Armand P, Gibson CJ, Cutler C, et al. A disease risk index for patients undergoing allogeneic stem cell transplantation. *Blood*. 2012;120:905–913.
20. Chang YJ, Zhao XY, Xu LP, et al. Donor-specific anti-human leukocyte antigen antibodies were associated with primary graft failure after unmanipulated haploidentical blood and marrow transplantation: a prospective study with randomly assigned training and validation sets. *J hematol Oncol*. 2015;8:84.
21. Ramsay NK, Kersey JH, Robison LL, et al. A randomized study of the prevention of acute graft-versus-host disease. *N Engl J Med*. 1982;306:392–397.
22. Rowlings PA, Przepiorka D, Klein JP, et al. IBMTR Severity Index for grading acute graft-versus-host disease: retrospective comparison with Glucksberg grade. *Br J Haematol*. 1997;97:855.
23. Pavletic SZ, Vogelsang GB, Lee SJ. 2014 National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: preface to the series. *Biol Blood Marrow Transplant*. 2015;21:387.
24. Liu DH, Liu KY, Xu LP, et al. Donor lymphocyte infusion for treatment of relapse of leukemia after HLA-mismatched hematopoietic stem cell transplantation. *Haematologica*. 2007;92:414.
25. Huang XJ, Liu DH, Liu KY, et al. Modified donor lymphocyte infusion after HLA-mismatched/haploidentical T cell-replete hematopoietic stem cell

transplantation for prophylaxis of relapse of leukemia in patients with advanced leukemia. *J Clin Immunol*. 2008;28:276–283.
26. McCurdy SR, Kanakry JA, Showel MM, et al. Risk-stratified outcomes of nonmyeloablative HLA-haploidentical BMT with high-dose posttransplantation cyclophosphamide. *Blood*. 2015;125:3024–3031.
27. Barker JN, Davies SM, Defor TE, et al. Determinants of survival after human leucocyte antigen-matched unrelated donor bone marrow transplantation in adults. *Br J Haematol*. 2015;118:101–107.
28. Carreras E, Jiménez M, Gómezgarcía V, et al. Donor age and degree of HLA matching have a major impact on the outcome of unrelated donor haematopoietic cell transplantation for chronic myeloid leukaemia. *Bone Marrow Transplant*. 2006;37:33.
29. Tamaki S, Ichinohe T, Matsuo K, Hamajima N, Hirabayashi N, Dohy H. Superior survival of blood and marrow stem cell recipients given maternal grafts over recipients given paternal grafts. *Bone Marrow Transplant*. 2001;28:375.
30. Randolph SS, Gooley TA, Warren EH, Appelbaum FR, Riddell SR. Female donors contribute to a selective graft-versus-leukemia effect in male recipients of HLA-matched, related hematopoietic stem cell transplants. *Blood*. 2004;103:347–352.
31. Kollman C, Howe CW, Anasetti C, et al. Donor characteristics as risk factors in recipients after transplantation of bone marrow from unrelated donors: the effect of donor age. *Blood*. 2001;98:2043–2051.
32. Baron F, Labopin M, Niederwieser D, et al. Impact of graft-versus-host disease after reduced-intensity conditioning allogeneic stem cell transplantation for acute myeloid leukemia: a report from the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *Leukemia*. 2012;26:2462.
33. Signori A, Crocchiolo R, Oneto R, et al. Chronic GVHD is associated with lower relapse risk irrespective of stem cell source among patients receiving transplantation from unrelated donors. *Bone Marrow Transplant*. 2012;47:1474.
34. McCurdy SR, Kanakry CG, Tsai HL, et al. Grade II acute GVHD and higher nucleated cell graft dose improve progression-free survival after HLA-haploidentical transplant with posttransplant cyclophosphamide. *Biol Blood Marrow Transplant*. 2017;24:343–352.
35. Saillard C, Crocchiolo R, Furst S, et al. National Institutes of Health classification for chronic graft-versus-host disease predicts outcome of allo-hematopoietic stem cell transplant after fludarabine-busulfan-antithymocyte globulin conditioning regimen. *Leuk Lymph*. 2014;55:1106.
36. Mo XD, Xu LP, Zhang XH, et al. Chronic GVHD induced GVL effect after unmanipulated haploidentical hematopoietic SCT for AML and myelodysplastic syndrome. *Bone Marrow Transplant*. 2015;50:127–133.
37. Mo XD, Xu LP, Zhang XH, et al. Haploidentical hematopoietic stem cell transplantation in adults with Philadelphia-negative acute lymphoblastic leukemia: No difference in the high- and low-risk groups. *Int J Cancer J*. 2015;136:1697–1707.
38. Nishiwaki S, Inamoto Y, Sakamaki H, et al. Allogeneic stem cell transplantation for adult Philadelphia chromosome-negative acute lymphocytic leukemia: comparable survival rates but different risk factors between related and unrelated transplantation in first complete remission. *Blood*. 2010;116:4368–4375.