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A Prospective Trial Comparing Haploidentical Donor Transplantation With Cord Blood Versus HLA-Matched Sibling Donor Transplantation for Hematologic Malignancy Patients

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Abstract

Although haploidentical donor (HID) hematopoietic stem cell transplantation (HSCT) has achieved similar survival to HLA-identical sibling donor (ISD) transplantation, the delayed hematopoietic engraftment as well as higher incidence of graft-versus-host-disease (GVHD), results in prolonged hospitalization, higher costs, and increased morbidity. In this study, a prospective, non-randomized clinical study was designed to evaluate the outcomes of patients who underwent HID HSCT supported by cord blood or ISD HSCT. Between May 2017 and November 2020, 113 patients were enrolled to undergo HID HSCT supported by cord blood (n=88) or ISD HSCT (n=25). The cumulative incidence of neutrophil and platelet engraftment at 30days was comparable in these two groups. Importantly, there was no significant difference in the cumulative incidence of grade II-IV aGVHD at 100days (20.5% [95% confidence interval [CI]: 12.2%–28.8%] versus 12.0% [95% CI: 0.2%–23.8%], $P = 0.32$) and cGVHD at 1 year (19.5% [95% CI: 11.2%–27.8%] versus 16.6% [[95% CI: 1.3%–31.9%] $P = 0.70$) between the two groups. Among the HID and ISD groups, the 2-year disease free survival was 76.8 and 80.0% ($P = 0.83$), the 2-year overall survival was 82.4 and 88.0% ($P = 0.66$), the 2-year GVHD-free, relapse-free survival was 68.9 and 75.3% ($P = 0.62$), respectively. Our results indicate that HID transplantation supported by cord blood may offer a good alternative to ISD HSCT for patients with hematopoietic malignancies. **Trial registration:** Effect of co-infusion third party umbilical cord blood stem cells on haploidentical hematopoietic stem cell transplantation https://www.chictr.org.cn Reg. No. ChiCTR-OIN-17011426.

Keywords

haploidentical donor, hematopoietic stem cell transplantation, cord blood, HLA-identical sibling donor, graft-versus-host disease

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) from a sibling donor is the preferred first choice of treatment for patients with hematopoietic malignancies. Unfortunately, only <30% patients have HLA-matched siblings. This is especially true in China, where the one-child policy has been implemented during the past three decades. Haploidentical donor (HID) transplantation provides an appealing option for patients who lack matched donors or require urgent transplantation. Furthermore, HID transplantation exhibits a stronger graft-versus-leukemia effect compared to HLA-identical sibling donor (ISD) transplantation[1]. Chang et al demonstrated that HID transplantation is superior to ISD transplantation for eradicating pre-transplantation MRD[2]. Although several studies have reported that HID transplantation achieved a similar survival to ISD transplantation, the

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delayed platelet engraftment, a high incidence of graft-versus-host-disease (GVHD), and non-relapse mortality (NRM) remain major problems after HID transplantation[3].

Cord blood as an alternative source of stem cells, has advantages of low incidences of GVHD and good graft-versus-leukemia activity[4]. To balance the potential benefits of the greater alloimmunity with the concern for increased in GVHD, some recent studies have combined haploidentical transplantation with third-party cord blood cells. This transplantation model could result in rapid engraftment, low incidences of GVHD, and relapse in patients with hematological malignancy[5-9]. Our group recently published a retrospective study that demonstrated that HID transplantation supported by cord blood resulted in a lower risk of relapse and prolonged progressive free survival compared with HLA-matched unrelated donor transplantation[10]. However, it is still unknown that whether HID HSCT supported by cord blood would be a good alternative to ISD HSCT for patients with hematopoietic malignancies. In this study, the outcome of HID HSCT supported by cord blood is prospectively compared with ISD HSCT.

Subjects and Methods

Study Design

A prospective non-randomized trial was conducted from May 2017 to November 2020. Patients were enrolled to undergo HID HSCT supported by cord blood ($n = 88$) or ISD HSCT ($n = 25$) according to donor availability. The primary end points were disease free survival (DFS) and NRM. Secondary end points were the incidence of aGVHD, the incidence of cGVHD, relapse rates, hematopoietic engraftment, and overall survival (OS). The cutoff date was November 25, 2021. This clinical trial was registered to www.chictr.org as ChiCTR-OIN-17011426.

Eligibility Criteria

The eligible patients ranged in age from 15 to 65 years with hematopoietic malignancies including acute myeloid leukemia, acute lymphoblastic leukemia (ALL), chronic leukemia, high-grade lymphoma, and high-risk myelodysplastic syndromes. All of the patients had transplantation indications and had received a myeloablative conditioning regimen. This study was approved by the Institutional Research and Ethics Committee of Tianjin First Central Hospital. It was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all of the patients or their legal guardians.

Donor Selection

If an HLA-ISD was unavailable, patients without an HLA-matched unrelated donor or whose disease state left insufficient time for an unrelated donor search were eligible for HID transplantation.

Procedure

High-resolution HLA typing was used for HLA-A, B, C, DRB1, and DQB1 to select donors. Donor peripheral blood stem cells were mobilized using G-CSF (5 μg/kg/day) for 5 days. In the HID group, the haploidentical stem cells were infused into the recipient on day 1 and cord blood on day 2. Cord blood units were selected based on the HLA typing and cell count. Cord blood and recipient were matched for 4–5/6 HLA loci and the minimum cell count was 1×10^7/kg nucleated cells.

The conditioning therapy for the HID group was as follows: For patients with myeloblastic and hybrid malignancies, Busulfan was given at a total dose of 8 mg/kg divided on days 9 to 7, anti-thymocyte globulin (ATG-F) at 4 mg/kg on days -7 to -4, cyclophosphamide at 40 mg/kg on days -6 and -5, fludarabine at 30 mg/m^2 on days -4 to -2, cytarabine at 4 g/m^2 day on days -4 to -2. For ALL patients, fractionated total body irradiation(TBI) was given at a dose of 8–10 Gy, cyclophosphamide at 40 mg/kg on days -7 and -6, ATG-F at 4 mg/kg on days -7 to -4, fludarabine at 30 mg/m^2 on days -4 to -2, and cytarabine at 4 g/m^2 on days -4 to-2.

The conditioning therapy for the ISD group was as follows: For patients with myeloblastic malignancies, Busulfan was given at a total dose of 8mg/kg divided on days -9 to -7, cyclophosphamide at 40 mg/kg on days -6 and -5, fludarabine at 30 mg/m^2 on days -4 to -2, cytarabine at 4 g/m^2 day on days -4 to -2. For ALL patients, fractionated TBI was given at a dose of 8–10 Gy, cyclophosphamide at 40 mg/kg on days -7 and -6, fludarabine at 30 mg/m^2 on days -4 to -2, and cytarabine at 4 g/m^2 on days -4 to-2.

GVHD Prophylaxis

The GVHD prophylaxis consisted of cyclosporineA, mycophenolate mofetil, and methotrexate. Cyclosporine A initiated on day -4 at a dose of 2.5 mg/kg/d as a continuous infusion. The dose was adjusted to a serum level of 200–250 ng/ml. Mycophenolate mofetil was given at 500 mg twice per day from day-5 until day +30. Moreover, methotrexate was administered at 15 mg/m^2 on day +1 and 10 mg/m^2 on days +3, +6, and +11 posttransplant.

Supportive Care

All patients received levofloxacin (200 mg twice per day) and albendazole before conditioning. Prophylactic posaconazole, acyclovir was administrated during the conditioning and immunosuppressive period. Trimethoprim/sulfamethoxazole was given at 0.96 g twice per day from 1 week before conditioning until three months after stopping immunosuppressive drugs.

Post-Transplantation Evaluations

The remission status and chimerism were evaluated every 2 weeks during the first month and every month thereafter. The chimerism analysis was conducted using multiplex polymerase chain recation (PCR) amplification of short tandem repeat as previously described[10]. Both peripheral blood and bone marrow chimerism studies were included. Cytomegalovirus (CMV) and EBV DNA were also detected every 1- or 2-weeks using PCR. aGVHD and cGVHD was scored based on the published criteria[11,12].

Statistical Analysis

Categorical variables were compared using X^2 testing and the continuous variables were tested using t tests. The incidence of engraftment, GVHD, relapse, and NRM were estimated using the cumulative incidence estimates to accommodate competing risks. DFS, OS and GVHD-free, relapse-free survival (GRFS) were estimated using the Kaplan–Meier method and compared using the log-rank test. Cox proportional hazards regression models were used to perform the multivariate analysis. A P-value less than 0.05 was considered statistically significant. R software (version3.1.2; http://www.r-project.org) and SPSS 19.0 (Chicago, IL, USA) were used for the statistical analyses.

Results

Patients and Graft Characteristics

Between May 2017 and November 2020, 113 patients were enrolled to undergo HID HSCT supported by cord blood (n = 88) or ISD HSCT (n = 25). The characteristics of the patients and donors prior to transplantation are summarized in Table 1. The baseline characteristics in the two groups were matched. The median follow-up periods for the surviving patients were 925 days (range: 265–1667 days) in the HID group and 840 days (range: 301–1688 days) in the ISD group.

The median counts of donor derived mononuclear cells in the HID group and the ISD group were 6.2×10^8/kg (range: 1.8–13.0) and 6.8×10^8/kg (range: 2.8–12.9). The median counts of donor derived $CD34^+$ cells in the HID group and the ISD group were 4.5×10^6/kg (range: 1.9–9.5) and 4.1×10^6/kg (range: 1.4–9.6), respectively. The infused mononuclear cell of the unrelated cord blood in the HID group was 1.5×10^7/kg and the infused $CD34^+$ cells of the cord blood was 0.5×10^5/kg.

Hematopoietic Recovery and Engraftment

At 30 days after transplantation, 97.6% of the surviving patients (83/85) in the HID group achieved full haploidentical chimerism. Among them, nine patients showed cord blood microchimerism on day +14 (1.1%, range: 0.2-4.9%), but this was superseded rapidly by stable engraftment of HID cells after day +30 (0%, range: 0.0%–4.8%). Only one patient had sustained detectable cord blood microchimerism until six months after transplantation. There are three patients died within 30 days after transplantation, one died due to infection at day +8, one died due to hepatic failure at day +24 and another died due to heart failure at day +18. Except for the three patients who died early due to transplant-related mortality, all achieved neutrophil engraftment at 30 days after transplantation, with a median time to engraftment of 12 days (range: 10–30, P = 0.98, Figure 1). The cumulative incidence of platelet engraftment at 30 days was 92.0% (95% confidence interval [CI]: 86.2%–97.9%, P = 0.59, Figure 1), with a median time to engraftment of 15 days (range: 8–62).

In the ISD group, 100% of the surviving patients (25/25) achieved full donor chimerism on day +30. The cumulative incidence of neutrophil engraftment in the surviving patients at 30 days was also 100%, with a median time to engraftment of 12 days (range: 11–22). The cumulative incidence of platelet engraftment at 30 days was 84.0% (95% CI: 68.6%–99.4%), with a median time to engraftment of 15 days (range: 9–34).

Immune Recovery of T Cells

We further investigate the immune reconstitution after transplantation in HID and ISD group (Figure 2). At 3 months after transplantation, the proportion of $CD4^+$ T cells in HID group were significantly lower than of ISD group and comparable by 6 months after transplantation. However, the absolute number of the $CD4^+$ T cells between the two groups were comparable. Furthermore, the proportion and absolute number of $CD3^+$ T cells and $CD8^+$ T cells in HID group was higher than that of ISD group at 6 months after transplantation, which indicated the cytotoxic T lymphocytes were expanded in HID group.

GVHD

At day 100 after transplantation, the cumulative incidence of aGVHD (grades II-IV) was 20.5% (95% CI: 12.2%–28.8%) in the HID group versus 12.0% (95% CI: 0.2%–23.8%) in the ISD group (P = 0.32, Figure3). Grades III-IV aGVHD was present in four patients in the HID group and one patient in the ISD group. The cumulative incidence of cGVHD at 1 year in the HID group was 19.5% (95% CI: 11.2–27.8%), which was comparable to the ISD group at 16.6% ([95% CI: 1.3%–31.9%] P = 0.70, Figure 3).

The variable which may influence the outcomes of transplantation was included in the COX model analysis. The included variables were donor type (HID vs ISD), disease (ALL vs AML/MDS), age (>40y vs ≤40y) and CIBMTR-DRI score. Backward elimination was used to identify

Table 1. Patient Characteristics.

	HID with cord blood	ISD	*P* value
Total patients	88	25	
Median age, y (range)	31.5 (15~64)	38 (17–63)	0.052
Male/female	57/31	13/12	0.246
Diagnosis			0.483
AML/MDS	43	16	
CR1	26	11	
CR2	3	4	
Other	14	1	
ALL	33	6	
CR1	23	5	
CR2	8	1	
Other	2	0	
HAL	2	0	
CR1	1	0	
CR2	1	0	
Other	10	3	
Cytogenetic characteristic			0.583
Normal	46	11	
t(8:21)	3	1	
-5/5q-	3	0	
-7/7q-	2	0	
+8	2	1	
Complex cytogenetic aberrations	5	3	
Ph	7	1	
Others	11	2	
Unavailable	9	6	
Molecular characteristic			0.501
Normal	16	4	
TP53	7	0	
FLT3-ITD	9	3	
MLL	4	3	
C-KIT	4	1	
CEBPA	4	3	
BCR-ABL	8	4	
Others	20	4	
Unavailable	16	3	
CIBMTR-DRI			0.146
Low	2	3	
Intermediate	57	17	
High	25	4	
Very high	4	1	
Conditioning regimens			
AML/MDS	Bu/Flu/Cy/Ara-C/ATG	Bu/Flu/Cy/Ara-C	
ALL	TBI/Flu/Cy/Ara/ATG	TBI/Flu/Cy/Ara-C	
HAL	Bu/Flu/Cy/Ara-C/ATG	-	
MNC ($\times 10^8$/kg)	6.2 (1.8–13.0)	6.8 (2.8–12.9)	0.117
$CD34^+$ ($\times 10^6$/kg)	4.5 (1.9–9.5)	4.1 (1.4–9.6)	0.179
Sex mismatch	35	10	0.984
ABO mismatch (Haplo or ISD)			0.480
Major	17	7	
Minor	14	5	
Major and minor	5	0	
Match	52	13	
HLA compatibility			0.00
Haplo HLA match			
5/10	66	0	
6/10	12	0	
7/10	7	0	
8/10	3	0	
ISD HLA match			
10/10	0	25	
CB MNC cells ($\times 10^7$/kg)	1.5 (0.8–2.7)	-	
CB CD34+ cells($\times 10^5$/kg)	0.5 (0.08–1.6)		

HID: haploidentical donor; ISD: identical sibling donor; AML/MDS: acute myeloid leukemia/myelodysplastic syndromes; ALL: acute lymphoblastic leukemia; CR: complete remission; HAL: hybrid acute leukemia; CEBPA: CCAAT enhancer binding protein alpha; FLT3-ITD: FMS-like tyrosine kinase-3 internaltandem duplication; CIBMTR-DRI:Center for International Blood and Marrow Transplantation Research-disease risk index; MNC: mononuclear cell; HLA: human leukocyte antigen; CB: cord blood; TBI: total body irradiation; ATG: anti-thymocyte globulin.

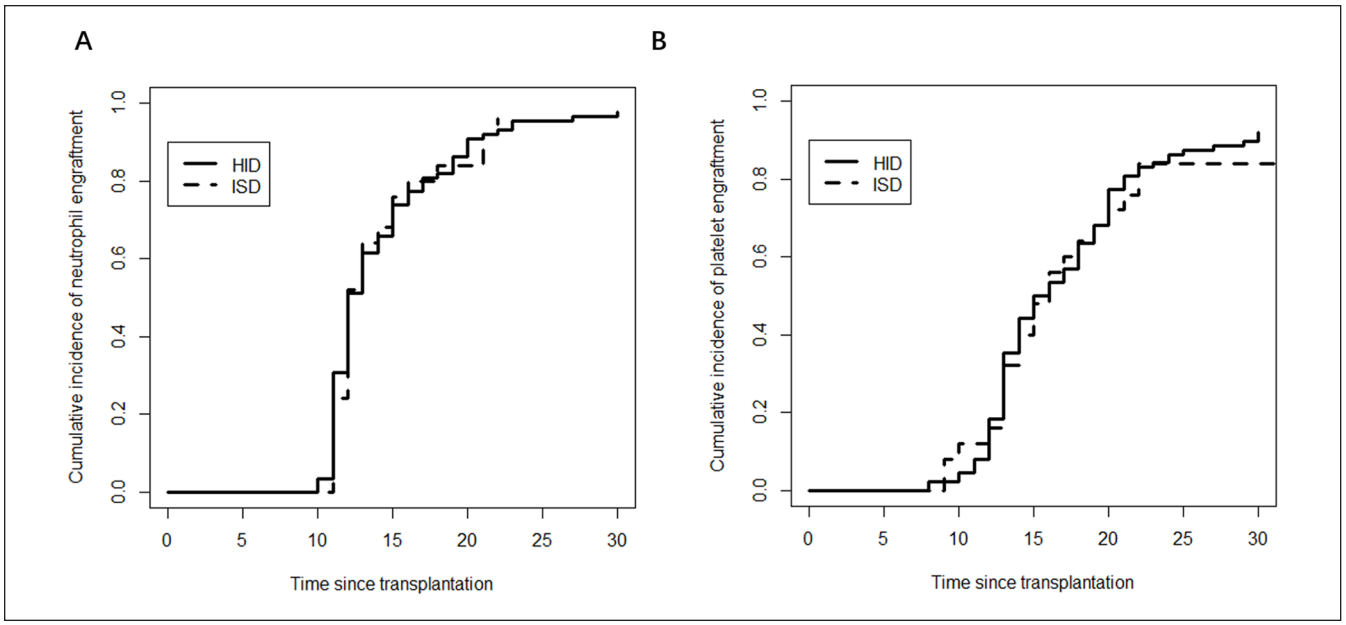

Figure 1. The hematopoietic engraftment after transplantation in the HID group and the ISD group. (A) cumulative incidence of neutrophil engraftment, and (B) cumulative incidence of platelet engraftment. HID: haploidentical donor, ISD: identical sibling donor.

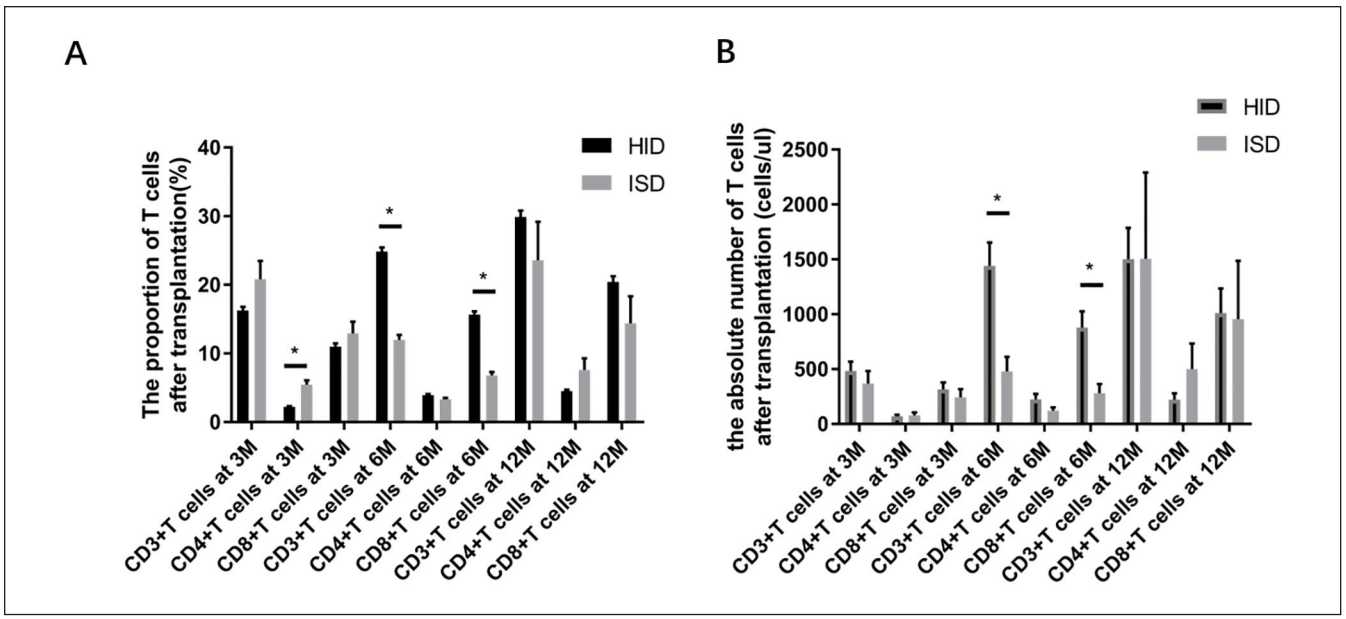

Figure 2. The proportion (A) and absolute number (B) of T cells after transplantation in the HID group and the ISD group. HID: haploidentical donor, ISD: identical sibling donor.

covariates that influenced outcomes. According to the multivariate analysis (Table 2), there was no significant difference in the risk of grades II-IV aGVHD (hazard ratio [HR] = 1.875; 95% CI = 0.552–6.365; P = 0.314) and cGVHD (HR=1.280; 95% CI: 0.404–4.056; P = 0.675) in the HID group relative to the ISD group.

Infections

By 1-year post HSCT, the HID group had a comparable incidence of CMV viremia (HID group 18.2% vs. ISD group 8%, P = 0.22) and EBV viremia (HID group 3.4% vs. ISD group 4.0%, P = 0.89) compared with ISD group. Furthermore, there was no statistical significance in the

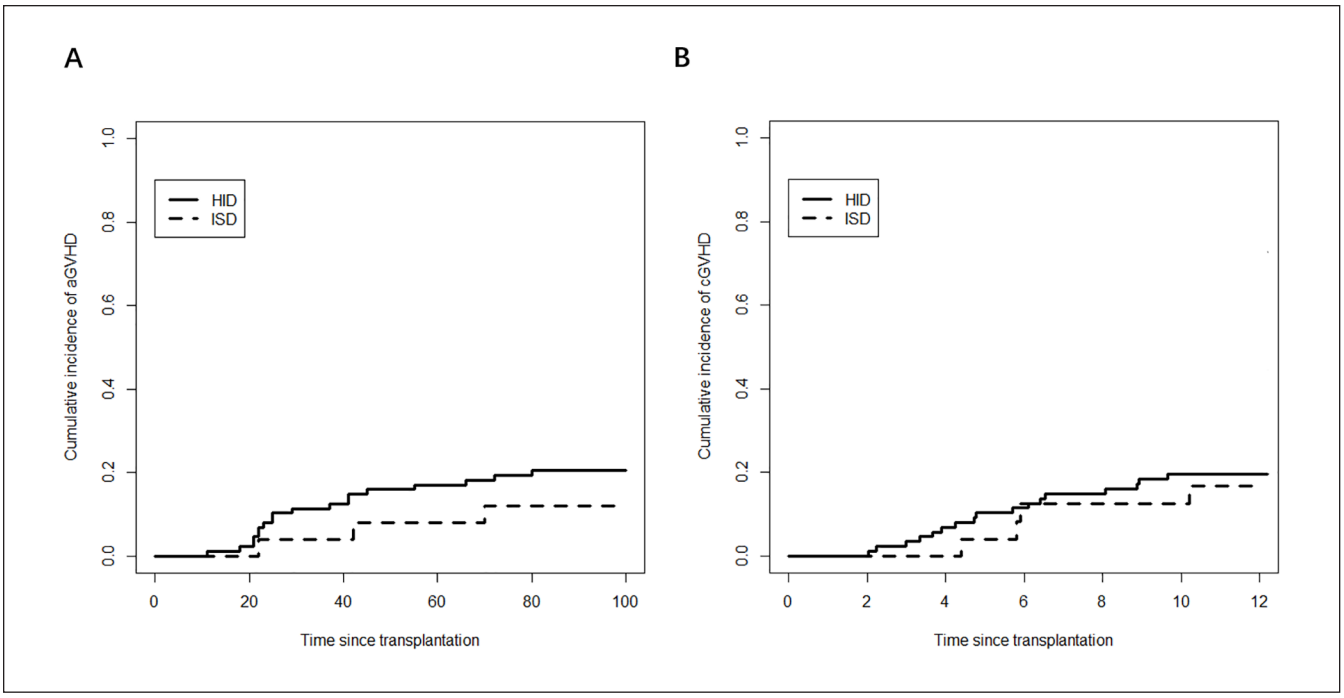

Figure 3. Cumulative incidence of grades II-IV aGVHD (A) and all grades of cGVHD (B) in the HID and ISD groups. GVHD: graft-versus-host-disease, HID: haploidentical donor, ISD: identical sibling donor.

incidence of probable and proven fungal infection (HID group 13.6% vs. ISD group 8.0%, $P = 0.45$).

NRM, Causes of Deaths and Relapse

The cumulative incidence curves are shown in Figure 4. The 2-year cumulative incidence of NRM in the HID group and the ISD group was 10.2% (95% CI: 2.6%–17.8%) and 8.0% (95% CI: 0.1%–15.9%, $P = 0.64$), respectively. In the HID group, non-relapse deaths were due to infection in three patient, cGVHD in two patients, hemorrhage in three patients, and toxicity in two patients. In the ISD group, non-relapse deaths were due to infection in one patient and hemorrhage in one patient. The 2-year cumulative incidence of relapse in the HID group was 14.2% (95% CI: 6.8%–21.5%), which is comparable to the ISD group 12.0% (95% CI: 0.3%–23.7%, $P = 0.71$). The multivariate analysis showed significant differences in relapse rates and the DFS between the different CIBMTR-DRI scores. However, there was no statistical difference in the relapse risk between the donor types (HR = 0.720; 95% CI: 0.194–2.675; $P = 0.623$, Table 2).

Survival

The OS at two years was 82.4% (95% CI: 73.8%–91.0%) for the HID group and 88.0% (95% CI: 76.2%–99.8%) for the ISD group ($P = 0.66$, Figure 5). The 2-year DFS for the HID patients was 76.8% (95% CI: 67.8%–85.8%), compared with 80.0% (95% CI: 64.3%–95.7%) for ISD patients ($P = 0.83$, Figure 5). Furthermore, the 2-year GRFS for the HID patients was 68.9% (95% CI: 59.1%–78.7%), compared with 75.3% (95% CI: 58.1%–92.5%) for ISD patients ($P = 0.62$, Figure 5). According to the multivariate analysis (Table 2), no difference in OS (HR = 0.892; 95% CI: 0.246–3.236; $P = 0.862$), DFS (HR = 0.818; 95% CI: 0.296–2.262; $P = 0.699$) and GRFS (HR 1.058; 95% CI: 0.428–2.619; $P = 0.903$) was seen in the HID with cord blood group relative to the ISD transplants.

Discussion

With the wide use of reduced-intensity conditioning, post-transplantation cyclophosphamide, ATG, and better supportive therapy, the survival of haploidentical transplantation has been largely improved. However, the delayed hematopoietic engraftment and high incidence of GVHD still remain significant challenges. In this prospective study, haploidentical transplantation was combined with cord blood, and it was found that it could achieve similar outcomes compared with ISD transplantation.

NRM is a significant cause of treatment failure after HID HSCT. According to the data during 2011–2015 from the European society of Blood and Marrow Transplantation, the NRM was higher with haplo-identical donor transplantation compared with ISD transplantations[1]. In this study, the 2-year NRM rate in the HID group was 10.2%, which was similar to contemporaneous patients undergoing ISD transplantation.

Table 2. Multivariate Analysis Results.

Outcome point	HR	95% CI	*P*
Acute GVHD			
Donor: HID vs ISD	1.875	0.552–6.365	0.314
Disease: ALL vs. AML/MDS	0.346	0.114–1.047	0.060
Age: >40y vs.≤40y	0.636	0.253–1.603	0.338
CIBMTR-DRI	1.221	0.597–1.603	0.585
Chronic GVHD			
Donor: HID vs ISD	1.280	0.404–4.056	0.675
Disease: ALL vs. AML/MDS	1.116	0.417–2.984	0.828
Age: >40y vs.≤40y	1.271	0.536–3.018	0.586
CIBMTR-DRI	0.819	0.400–1.678	0.586
NRM			
Donor: HID vs ISD	1.108	0.233–5.258	0.898
Disease: ALL vs. AML/MDS	4.349	1.068–17.714	0.040
Age: >40y vs.≤40y	4.469	1.376–14.519	0.013
CIBMTR-DRI	1.149	0.408–3.234	0.792
Relapse			
Donor: HID vs ISD	0.720	0.194–2.675	0.623
Disease: ALL vs. AML/MDS	0.777	0.189–3.194	0.726
Age: >40y vs.≤40y	0.493	0.157–1.547	0.226
CIBMTR-DRI	2.949	1.528–5.692	0.001
OS			
Donor: HID vs ISD	0.892	0.246–3.236	0.862
Disease: ALL vs. AML/MDS	1.958	0.618–6.200	0.253
Age: >40y vs.≤40y	2.649	0.974–7.200	0.056
CIBMTR-DRI	1.743	0.807–3.765	0.157
DFS			
Donor: HID vs ISD	0.818	0.296–2.262	0. 699
Disease: ALL vs. AML/MDS	1.336	0.486–3.668	0.574
Age: >40y vs.≤40y	1.114	0.475–2.612	0.805
CIBMTR-DRI	2.114	1.156–3.865	0.015
GFRS			
Donor: HID vs ISD	1.058	0.428–2.619	0.903
Disease: ALL vs. AML/MDS	0.807	0.337–1.932	0.630
Age: >40y vs.≤40y	1.453	0.719–2.938	0.298
CIBMTR-DRI	1.653	0.970–2.818	0.065

CI: confidence interval; GVHD: graft-versus-host-disease; HID: haploidentical donor; ISD: identical sibling donor; non-relapse mortality; OS: overall survival; DFS: disease free survival; GRFS: GVHD-free, relapse-free survival; AML/MDS: acute myeloid leukemia/myelodysplastic syndromes; CIBMTR-DRI: Center for International Blood and Marrow Transplantation Research-disease risk index.

These data were comparable with previous studies about HID transplantation supplied with cord blood[5]. However, the cumulative incidence of NRM in this study was similar to some studies using the HID graft alone[3]. Several factors may contribute to the hidden advantages. First, the maximum age of these patients was older than in the other studies. Second, the proportion of patients with high-risk features and high HCT-CI scores was also higher. These characteristics may have been attributed to the higher NRM rate of both of the two groups in this study. Third, the composition of the disease entities was different from previous studies, which made it hard to compare these results with other studies.

Several studies have reported that HID transplantation combined with third-party cord blood cells could result in rapid engraftment, low incidences of GVHD and disease relapse[5,7,13–16]. In our past experience, the cumulative incidences of II-IV aGVHD and cGVHD in HID HSCT alone were 33.3% and 40%, respectively, which was higher than HID transplantation supported by cord blood[10]. In this analysis, the incidence of grades II-IV aGVHD in haploidentical transplantation combined with cord blood was 20.5%, which was also lower compared with historical data of HID HSCT alone. It was also lower than the reported results of haploidentical transplantation with post-transplantation cyclophosphamide or ATG[17]. Some studies revealed that patients receiving HID transplantation have a slower hematopoietic engraftment, higher incidence of aGVHD and inferior survival compared to ISD transplantation[18]. In our study, by

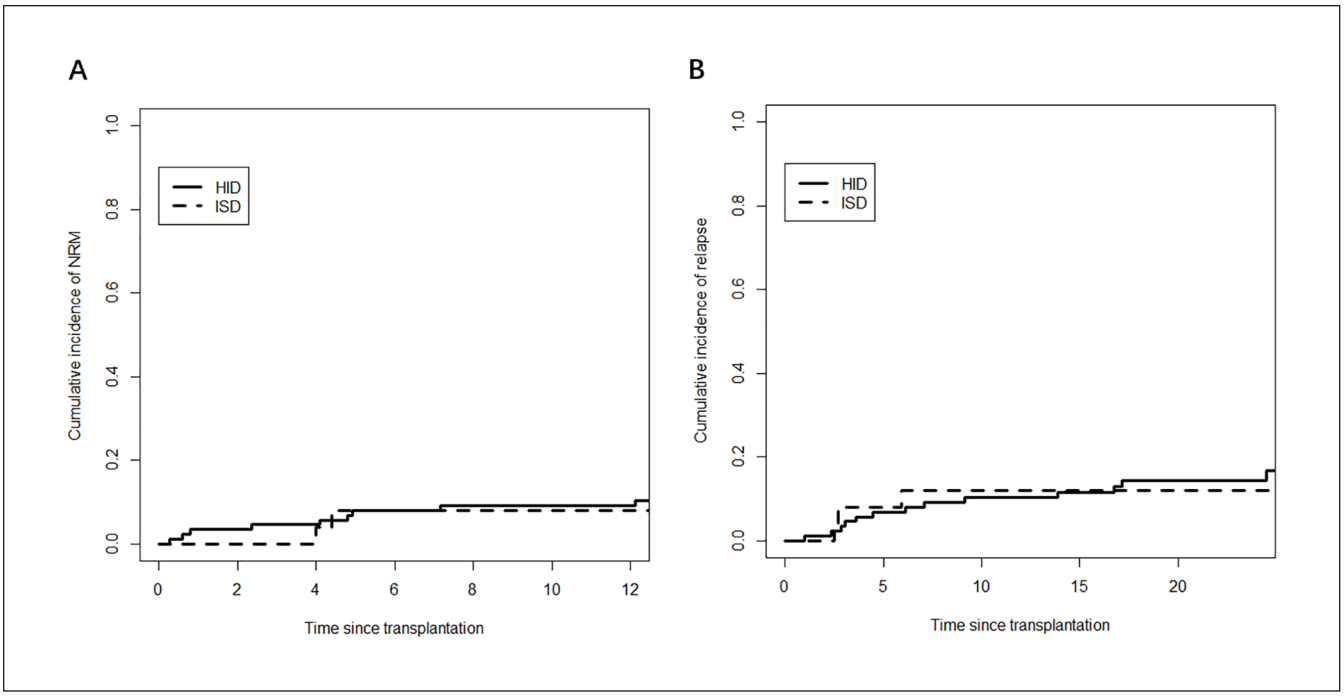

Figure 4. Comparisons of outcomes between the HID group and the ISD group. (A) cumulative incidence of NRM, (B) cumulative incidence of relapse. HID: haploidentical donor, ISD: identical sibling donor, NRM: non-relapse mortality.

combination of haploidentical and cord blood graft, the incidence of aGVHD was similar to the ISD transplantation. A possible mechanism may have been the higher proportion of T regulatory cells in cord blood, which may reduce the immune response. From another perspective, the main composition of T cells in cord blood is naïve T cells, which may also lead to a superior graft-versus-leukemia effect. Our previous work found that HID transplantation combined with cord blood resulted in a lower relapse rate and favorable progressive free survival compared to HLA-identical unrelated donor transplantation. In this study, no statistical significance was found for the relapse rate or the DFS between the HID and ISD groups. This may have been due to the short follow-up time, small sample size, and disease heterogeneity.

In this study, all of the patients in the HID group finally achieved haploidentical engraftment. This result was different with cord blood transplantation combined with haploidentical CD34+ cells, which had sustained cord blood engraftment[19,20]. Several factors likely contributed to the different outcomes. First, the amount of infused cord cells in this study was lower than in the cord blood transplantation. Second, the infused haploidentical cells in the cord blood transplantation was CD34 selected. The lack of haplo-identical T cells may have led to an engraftment failure of the haploidentical cells. In our study, there are nine patients who had a minority fraction of cord blood chimerism after HID transplantation. It seemed that the infused CD34 dose from haploidentical donor, the infused dose of cord blood cells and the degree of HLA matching between the haplo-graft and the host may contribute to the pattern of engraftment[21,22]. However, we did not find a significant difference of infused donor cell dose, the degree of HLA matching between the nine patients and other patients. It should also be noted that none of the nine patients relapsed and only one suffered grade II-IV aGVHD after transplantation. It seemed that cord blood microchimerism may induce immune tolerance, which decreased the incidence of aGVHD without compromising graft-versus-leukemia effect.

It has been shown that the incidence of infection after HID HSCT is higher than HLA-matched transplantation due to the delayed immunologic reconstitution[23,24]. It is especially apparent in HID transplantation with ATG-based regimens[25]. The higher incidence of infection increases the mortality rate, days of hospitalization and extra costs. By combination of cord blood with HID transplantation, we found that the incidence of infection in HID transplantation was similar to ISD transplantation. The rapid hematopoietic recovery and immunologic reconstitution might contribute to the favorable outcome. Moreover, other complications after transplantation were also comparable between the two groups, such as hepatic veno-occlusive disease, diffuse alveolar hemorrhage, periengraftment respiratory distress syndrome, kidney injury, and so on.

The main limitation of this study was the non-randomized design and small sample size, which was due to the ethical and practical reasons. The availability of a matched donor might have minimized this limitation to some extent. Furthermore, the imbalanced factors were adjusted using a

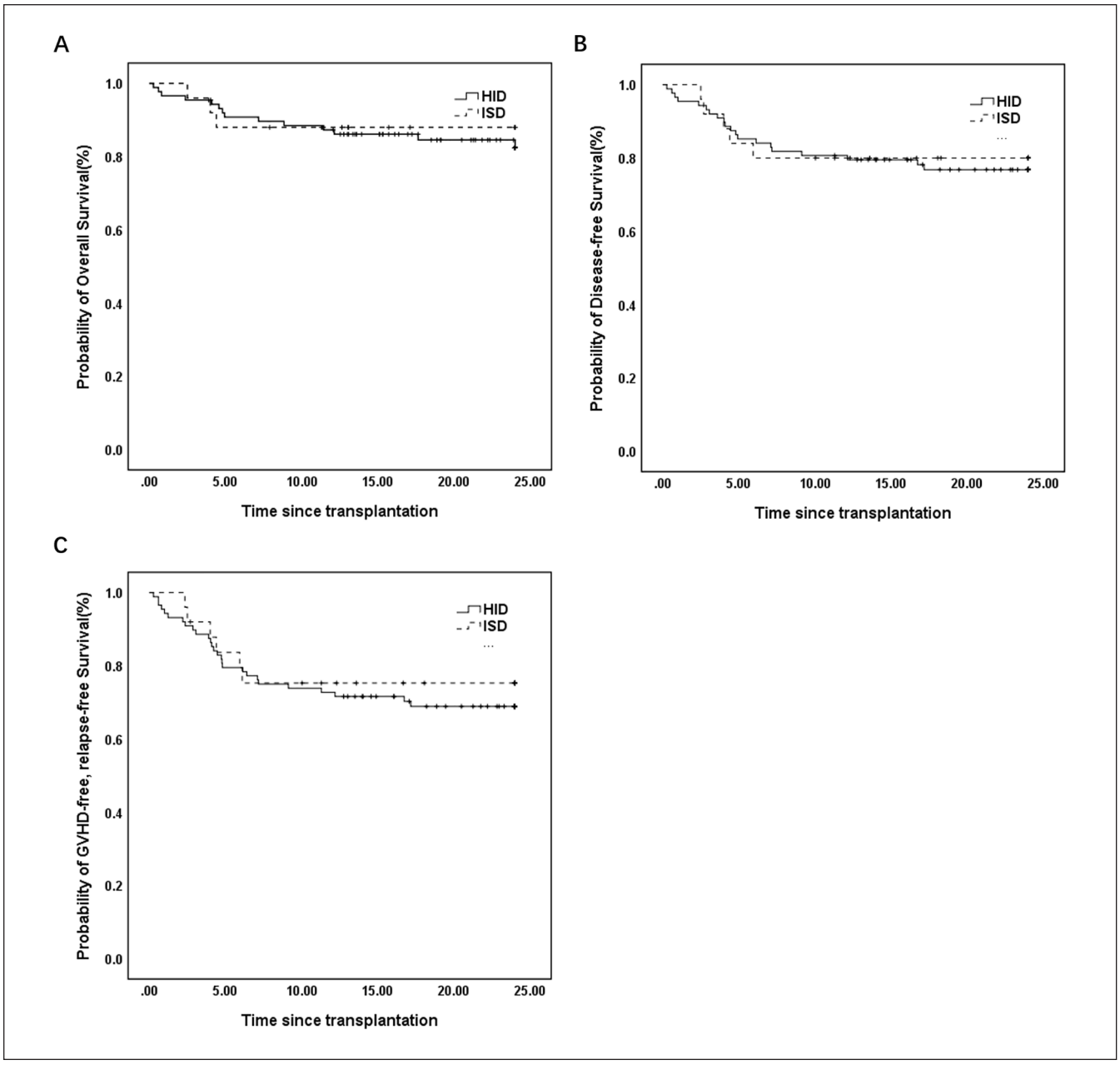

Figure 5. The Kaplan-Meier estimate of the probability of OS (A), DFS (B) and GRFS (C) in the HID and ISD patients. OS: overall survival, DFS: disease free survival; HID: haploidentical donor, ISD: identical sibling donor, NRM: non-relapse mortality; GFRS: GVHD-free, relapse-free survivl.

multivariate analysis. However, the influence of imbalanced factors on outcomes between the two cohorts cannot be totally eliminated. Thus, a large-scale, multicenter, prospective, randomized study is needed. The other important limitation was the unequal sample size between the two group. As the one-child policy was carried out in China in the past three decades, the number of patients who can find an ISD in China was less than that in other countries. On the contrary, it is easy to find an eligible HID. Thus, the number of patients in HID group in our study was higher than that in ISD group. When trying to infer from experience in previous studies of ISD transplantation, we found that the disease entities in our study was different from those studies[8,26,27]. Therefore, it is unsuitable to compare our studies with those studies. However, in our study, the baseline characteristics between the two group were not significantly different. Furthermore, we have adjusted the imbalanced factors by multivariate analysis. These efforts may minimize the imbalance between the two groups.

In summary, this study indicated that haploidentical transplantation combined with cord blood could result in similar outcomes compared with ISD transplantation. Thus, it is a

good alternative to ISD transplantation for patients with hematopoietic malignancies. Further large-scale, randomized, multicenter clinical trials should be to conducted to confirm the findings.

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Ethical Approval

This study was approved by the Institutional Research and Ethics Committee of Tianjin First Central Hospital.

Statement of Human Rights

This study was approved by the Institutional Research and Ethics Committee of Tianjin First Central Hospital. It was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all of the patients or their legal guardians.

Statement of Informed Consent

Informed consent was obtained from all of the patients or their legal guardians.

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