Clinical Cancer Research

Haploidentical versus Matched-Sibling Transplant in Adults with Philadelphia-Negative High-Risk Acute Lymphoblastic Leukemia: A Biologically Phase III Randomized Study

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Abstract

Purpose: Although matched-sibling donor (MSD) hematopoietic stem-cell transplantation (HSCT) has an established role in the management of adults with acute lymphoblastic leukemia (ALL) in first complete remission (CR1), the effect of haploidentical donor (HID) HSCT as post-remission treatment for this portion of patients is not defined.

Experimental Design: Transplantation outcomes from HIDs or MSDs were compared in a disease-specific, biologically phase III randomized, multicenter study. Between July 2010 and December 2013, 210 patients with Philadelphia-negative high-risk ALL in CR1 were assigned to undergo unmanipulated HIDs (121 patients) or MSDs HSCT (89 patients) according to donor availability on an intent-to-treat (ITT) basis.

Results: Overall, 24 of the 210 patients had lost transplant eligibility. Therefore, 186 of 210 (88%) patients were finally transplanted from MSD ($n = 83$) or HID ($n = 103$). Based on the ITT principle, the 3-year disease-free survival (DFS) did not differ between HID and MSD groups [61%, 95% confidence interval (CI), 52%–70%; vs. 60%, CI, 49%–71%; $P = 0.91$] from CR, neither did DFS differ between the two groups (68%, CI, 58%–78%; vs. 64%, CI, 52%–76%; $P = 0.56$) from time of the graft, with cumulative incidence of nonrelapse mortality of 13% (CI, 7%–19%) and 11% (CI, 4%–18%; $P = 0.84$) and relapse rates of 18% (CI, 10%–26%) and 24% (CI, 14%–34%; $P = 0.30$), respectively.

Conclusions: Haploidentical HSCT achieves outcomes similar to those of MSD-HSCT for Philadelphia-negative high-risk ALL patients in CR1. Such transplantation could be a valid alternative as post-remission treatment for high-risk ALL patients in CR1 lacking an identical donor. *Clin Cancer Res; 22(14); 3467–76. ©2016 AACR.*

Introduction

Previous studies have demonstrated that HLA-matched hematopoietic stem cell transplantation (HSCT) performed during the first complete remission (CR1) is superior to chemotherapy or autologous HSCT in the treatment of acute lymphoblastic leukemia (ALL; refs.1–3). Especially poor outcomes are seen in patients with high-risk characteristics treated with chemotherapy alone, such as age older than 35 years, high WBC count at diagnosis and unfavorable chromosome rearrangements (3–5). A meta-analysis demonstrated that when only high-risk patients were included, survival advantage with transplant over chemotherapy was even greater (3). Thus, HSCT from HLA-matched donors has become the standard of care for such high-risk patients.

Recent progress in haploidentical donor (HID) transplantation provides the benefits of rapid and near-universal donor availability (6–8). Our recent single-institute, retrospective study showed that haploidentical HSCT was superior to chemotherapy alone for patients with high-risk ALL in CR1 (9). However, in cases of where no HLA-matched donor is available, prospective and probably multicenter collaboration is required to define further the role of haplo-HSCT as post-remission therapy in this disease. Undoubtedly, randomized trials are needed to determine if haploidentical transplantation is, in fact, superior to chemotherapy for ALL in CR1. Nonetheless, this may be difficult to determine in this setting due to ethical and practical reasons given the inferior outcomes observed after chemotherapy-based post-remission strategies compared with those after allo-HSCT (1–3).

Given that HLA-matched transplant is the first choice in patients with high-risk adult ALL, and prior analyses demonstrated similar survival after haploidentical HSCT versus matched-sibling donors (MSD) HSCT for all hematological malignancies (10, 11) as well as for acute myeloid leukemia (AML) patients in CR1 (12), with regard to the specific, homogenous disease of

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Translational Relevance

This study demonstrates that, for every major transplant end point, including relapse, non-relapse mortality and survival, haploidentical and identical-sibling hematopoietic stem cell transplantations are not significantly different in patients with Philadelphia-negative high-risk acute lymphoblastic leukemia (ALL) in first complete remission (CR1). Thus, it provides a valuable alternative donor choice for post-remission treatment in Philadelphia-negative high-risk ALL.

Philadelphia (Ph)-negative high-risk ALL in CR1, the results from haploidentical HSCT have never been compared with those from MSDs to evaluate the value of haploidentical HSCT, either with T-cell depletion (TCD) or T-cell replete modality. To address this issue, we initiated the current biologically phase III randomized, multicenter, disease-specific study to compare the outcomes of consecutive Ph-negative high-risk ALL patients in CR1 undergoing haploidentical HSCT with all contemporaneous MSDs HSCT. Meanwhile, we also aimed to identify the pretransplantation patient-, donor-, and transplantation-related risk factors that affect the probability of survival.

Materials and Methods

Study design

Outcomes of HSCTs from MSDs and HIDs in adults with high-risk ALL were prospectively compared. Patients were assigned to undergo haploidentical or MSDs HSCT according to donor availability. Enrolment began in July 2010 and ended in December 2013 at three transplant centers in China (Peking University, $n = 130$; Soochow University, $n = 56$; Southern Medical University, $n = 24$). The study was performed in accordance with the Declaration of Helsinki and was approved by the local institutional review board. All donors and recipients gave written informed consent before enrolment. This study was registered as ChiCTR-OCH-10000940 at http://www.chictr.org.cn/abouten.aspx.

Patient eligibility criteria

Eligible patients were ages 18 to 60 years and had Ph-negative high-risk ALL in CR1 with no contraindications to HSCT. Patients were classified as high risk if they met one of the following criteria at diagnosis: (i) adverse cytogenetics (t[4;11], low hypodiploidy-near triploidy, or complex karyotype [≥5 abnormalities]; (ii) older age (≥35 years); (iii) high leukocyte counts (≥30 × 10^9/L for B precursor ALL or ≥100 × 10^9/L for T-precursor ALL); or (iv) delayed CR1 (remission required more than 28 days of induction therapy; refs.13 and14).

Donor selection

HLA-matched sibling donor was the first choice for allo-transplantation. If an HLA-matched sibling donor was unavailable, subjects without a suitable closely HLA-matched unrelated donor (URD; >8 of 10 matching HLA-A, B, C, DR, and DQ loci and >5 of 6 matching HLA-A, B, and DR loci) after 2 cycles of consolidation were eligible for HLA-haplotype transplantation. For this comparative analysis to arrive at comparable patient cohorts that received transplants during the same time interval, we excluded patients who received URD HSCT ($n = 16$). The protocol required DNA typing of the patient and donor at intermediate resolution for HLA-A, B and at high resolution for DRB1. HID subjects received a graft from a family member sharing one HLA haplotype with the recipient but differed to a variable degree for the HLA-A, B, and DR antigens of the unshared HLA haplotype.

Chemotherapy prior to HSCT

For the induction of a complete remission, patients received chemotherapy in accordance with the national ALL-protocols, which included VDCLP (vincristine, daunorubicin, cyclophosphamide [Cy], L-asparaginase and prednisone), VDCP, VDLP, or VDP. Consolidation chemotherapy regimens included Hyper-CVAD (A) (Cy, doxorubicin, vincristine, and dexamethasone), Hyper-CVAD (B) (methotrexate [MTX] and cytosine arabinoside [Ara-c]), MTX+L-asparaginase or CAM (Cy, Ara-c and mercaptopurine), which were given in turn. Patients who did not achieve CR after induction received re-induction chemotherapy, which included VDCP, VDCLP, MAE (Ara-C, mitoxantrone, and etoposide); MTX+L-asparaginase or Hyper-CVAD (B). Patients received re-induction chemotherapy according to doctors' experience and patients' intension. Prophylaxis of central nervous system leukemia consisted of intrathecal chemotherapy with MTX, Ara-c, and dexamethasone for at least six doses during induction chemotherapy and consolidation chemotherapy. The two study groups did not differ in the inductions they received ($P = 0.52$).

Transplant procedures

Granulocyte colony-stimulating factor (G-CSF; 5 μg per kilogram of body weight per day for 5 days) was used to mobilize the bone marrow (G-BM) and peripheral blood (G-PB). The target mononuclear cell count (MNC) was more than 6×10^8 per kilogram of recipient weight. Unmanipulated BM (harvested on day 4 after G-CSF) and PB stem cells (PBSCs, harvested on day 5 after G-CSF) were infused into the recipient on the day of collection. All HID patients received both G-BM and G-PB (G-BMPB).

The conditioning therapy for the HID group was as follows: cytarabine (4 g/m^2/d) intravenously on days −10 to −9; busulfan (3.2 mg/kg/d) intravenously on days −8 to −6; cyclophosphamide (1.8 g/m^2/d), intravenously on days −5 to −4; Me-CCNU (250 mg/m^2/d), orally once on day −3; and ATG (thymoglobulin, 2.5 mg/kg/d, Sang Stat) intravenously on days –5 to –2. The majority of patients in the MSD group received hydroxycarbamide (80 mg per kilogram) orally on day –10 and a lower dose of cytarabine (2 g/m^2/d) on day −9, but otherwise, an identical regimen to the HID patients without ATG was used. A small part of MSD patients were conditioned with total body irradiation (TB1, 770cGy) and cyclophosphamide. Graft-versus-host-disease (GVHD) prophylaxis regimen consisted of cyclosporine A (CsA), mycophenolate mofetil (MMF), and short-term methotrexate (11).

After completion of the study treatment, bone marrow samples were analyzed at 1, 2, 3, 4.5, 6, 9, and 12 months after transplantation and at 6-month intervals thereafter for the monitoring of minimal residual disease (MRD), defined as previously reported (15, 16). In Peking University, modified donor lymphocyte infusion (DLI) would be given before hematological relapse as the intervention therapy (preemptive DLI) after 3 months after HSCT following a trial of immunosuppressant withdrawal. The detailed criteria for preemptive DLI administration included: (i) patients scored as MRD+ if they had two consecutive positive

results using flow cytometry (FCM) or Wilms' tumor gene 1 (WT1) or were both FCM+ and WT1+ in a single sample within 1 year after transplantation; (ii) no uncontrolled GVHD or life-threatening infection; and (iii) with donor availability and willingness. Patients with GVHD first received GVHD therapy, and after GVHD was controlled, MRD testing was repeated and those patients remained MRD+ received modified DLI. In total, 10 patients (5 HID and 5 MSD) required this preemptive approach, which occurred at a median of 153 days (range, 88–260 days) after transplantation. The modified DLI regimen was previously described (17). When a hematologic relapse was diagnosed after HSCT, post-transplant immune suppression was immediately discontinued. If patients did not develop GVHD within 2 weeks and if patients agreed to receive targeted therapeutic modified DLI and their donors also agreed to undergo peripheral blood stem cell collection again, patients would receive chemotherapy followed by modified DLI; otherwise, patients would receive chemotherapy alone (18). Anti-leukemia chemotherapy before DLI included MTX (1.0–1.5 g/m^2/d for a single dose) or CODP (cyclophosphamide 800 mg/m^2/d for 2 d, vincristine 1 mg/m^2/d for a single dose, daunorubicin 40 mg/m^2/d for 3 d, and prednisone 60 mg/d for 7 d). In total, 19 patients (12 HID and 7 MSD) were given this targeted therapeutic DLI (see Results). The median number of CD3$^+$ cells infused in each patient was 0.56 (range, 0.15–2.01) $\times$ 10^8/kg. Chimerism analyses were done by DNA fingerprinting of short-tandem repeat on blood samples.

Statistical analysis

Disease-free survival (DFS) was the primary objective, taking the date of achieving CR as the starting point for the whole study population in intent-to-treat (ITT) analysis and also the date of HSCT as the starting point for patients finally transplanted, and the date of the first event or of the last follow-up as the end of the interval. Endpoint events for DFS included morphologic relapse and death from any cause in CR1. Patients with MRD were not considered relapse for DFS determination. Other endpoints included overall survival (OS) and relapse rates. Death from any cause was used as an event for OS, and survivors were censored at the date of the last follow-up. Relapse was defined as recurrence of BM blasts >5%, reappearance of blasts in the blood, or development of extramedullary disease infiltrates at any site. Non-relapse mortality (NRM) was defined as death from any cause in the first 28 days after HSCT or death without evidence of disease recurrence beyond day 28. Assessments of engraftment and chimerism were previously described in detail (11). Chronic GVHD was classified as limited or extensive and was also classified as mild, moderate, or severe by the National Institutes of Health consensus criteria. GVHD were evaluated and graded by a single practitioner within the program.

Comparisons of patient characteristics between the two groups were performed using the Mann–Whitney test for continuous variable and χ^2 test for categorical data. Survival functions were estimated using the Kaplan–Meier method and compared by the log-rank test. Cox proportional hazards regression models were used to evaluate the relative risk of subjects receiving either allotransplant by forcing the main interest variable (HID vs. MSD, using MSD as the reference group) into the model. Backward elimination with a criterion of $P < 0.10$ for retention was used to select a final model. The following variables were analyzed: age at transplantation (<30 years vs. 30–39 years vs. 40–49 years vs. $\geq$50 years) treated in each additional decade as referenced by Marks and colleagues (19), sex (female or male), time from diagnosis to HSCT (<6 months vs. $\geq$6 months), donor–recipient sex match (female–male vs. others), chronic GVHD (cGVHD; negative vs. limited cGVHD vs. extensive cGVHD), TBI (yes vs. no), and graft source (BM or PB vs. both). Transplant centers were also included in the model. The assumption of proportional hazards for each factor in the Cox model was tested. The test indicated that the proportionality assumptions hold. Two-way interactions were checked between each selected variable and the main effect variable; no significant interactions were detected. Relapse, non-relapse mortality (NRM), engraftment, and GVHD were estimated as cumulative incidences, taking into account competing risks, with relapse treated as a competing event to calculate NRM, and with death from any causes as a competing risk for GVHD, engraftment, and relapse. Associations between donor type and outcome were evaluated using an add-on package for the R statistical software, which allows for the estimation of the semiparametric proportional hazards model for the sub-distribution of a competing risk analysis (20). The SAS software, version 9.4 (SAS Institute), and R statistical software (Bell Labs) were used for data analyses.

Results

Characteristics of study patients

Between July 2010 and December 2013, 210 patients with Ph-negative high-risk ALL in CR1 were assigned to undergo unmanipulated HIDs (121 patients) or MSDs HSCT (89 patients) according to donor availability on an ITT basis. Overall, 24 of the 210 patients had lost the transplant eligibility. Therefore, 186 of 210 (88%) patients were finally transplanted from MSD (n = 83) or HID (n = 103). A CONSORT flow diagram starting with subjects eligible a transplant is shown in Fig. 1. Patient characteristics are shown in Table 1. The two groups were balanced except that patients undergoing HID-HSCT were significantly younger, got marrow and blood both, not getting TBI. The analysis includes data collected as of December 31, 2014. The median follow-up for surviving patients is 1,110 days (range, 210–1,848 days) after achieving CR for all the eligible patients and 1,031 days (range, 370–1,638 days) after HSCT for the finally transplanted patients.

Engraftment and GVHD

Neutrophil engraftment was comparable between the two groups (Table 2). All except one patient in each group achieved donor-cell engraftment. Platelet recovery was faster in the MSD cohort (Table 2). The rates of acute GVHD (aGVHD) and chronic GVHD (cGVHD) were shown in Table 2 and Fig. 2. For the HID group, the cumulative incidence of aGVHD or cGVHD did not vary with HLA disparities (3/6 or 4–5/6 matches: 27% vs. 38%, P = 0.25; 36% vs. 47%, P = 0.34). Stem cell source did not influence the incidence and severity of cGVHD after MSD-HSCT (data not shown). The 3-year cumulative incidence of extensive GVHD did not vary between patients older than 30 years and younger patients (10% vs. 12%, P = 0.60) or between female to male and other sex pairs (12% vs. 12%, P = 0.99).

Relapse, NRM, and survival on ITT basis

Based on the ITT analysis, the 3-year cumulative incidences of relapse (CIR) were 28% (CI, 19–37) and 26% (CI, 17–35; P = 0.86) among HID and MSD patients. The 3-year DFS rate after HID-HSCT was similar to that after MSD-HSCT (61%; CI, 52–70

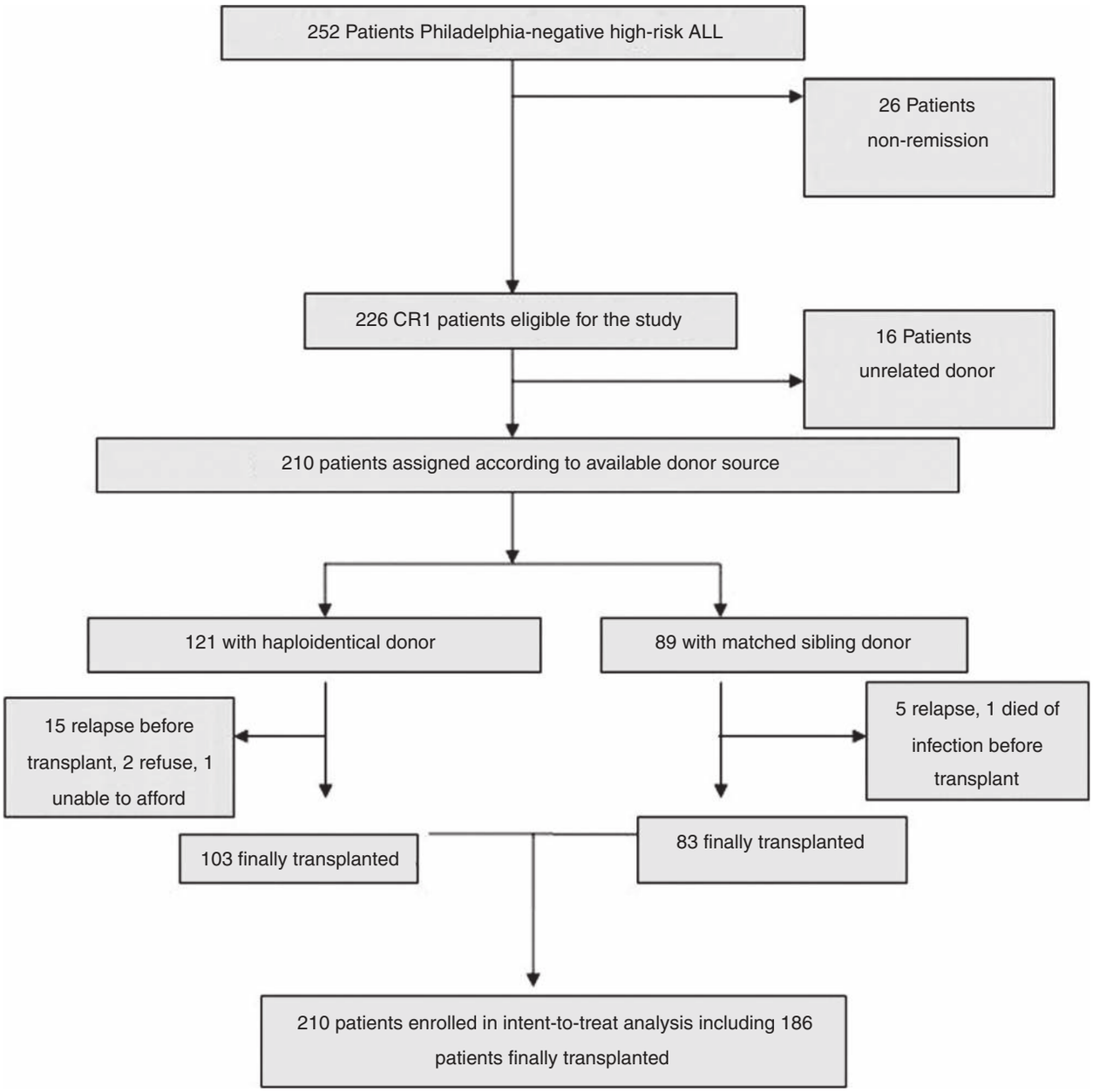

Figure 1.
Patient recruitment.

vs. 62%; CI, 52–72; $P = 0.91$). No significant differences in OS [3-year rate, 68% (CI, 59–77) vs. 66% (CI, 56–76); $P = 0.81$] or NRM rates [3-year cumulative incidence, 11% (CI, 6–16) vs. 12% (CI, 5–19); $P = 0.76$] were observed after HID-HSCT and after MSD-HSCT.

Relapse, NRM, and survival after transplant

At Peking University, 10 patients (5 HID and 5 MSD) required preemptive DLI as intervention for positive MRD, which occurred at a median of 153 days (range, 88–260 days) after transplantation. Until the last follow-up, 17 (16%) and 19 (23%) patients experienced relapse after HID- or MSD-HSCT. In total, 19 patients (12 HID and 7 MSD) were given targeted therapeutic DLI after relapse. Results of preemptive DLI, rates of relapse, and outcomes of different therapy after relapse are listed in Table 2. The 3-year CIR were 18% (CI, 10–26) and 24% (CI, 14–34; $P = 0.30$) among HID and MSD patients (Table 2; Fig. 3A). Multivariate analysis failed to show significant differences in CIR between the two cohorts (Table 3). No differences in CIR were found between patients with or without adverse cytogenetics (28% vs. 19%, $P = 0.27$) or between MSD-HSCT with TBI-based regimen or non-TBI regimen (37% vs. 20%, $P = 0.11$).

Table 1. Patient and graft characteristics[a]

Characteristics	Haploidentical ($N = 121$)	Matched sibling ($N = 89$)	*P*
Age, years median (range)	26 (18–59)	38 (18–59)	<0.001
<30	73 (60)	30 (34)	0.001
30–39	20 (17)	17 (19)	
40–49	22 (18)	32 (36)	
>50	6 (5)	10 (11)	
Older age (≥35)	39 (32)	53 (60)	<0.001
Gender, male, *n* (%)	72 (59)	47 (53)	0.33
Lineage, *n* (%)			0.84
B	91 (75)	68 (76)	
T	30 (25)	21 (24)	
Median white blood cell count /mm^3	30.0 (1.2–428.2)	28.8 (0.8–697.1)	0.71
High white blood cell count[b], *n* (%)	51 (42)	38 (43)	0.93
Adverse cytogenetic risk, *n* (%)	22 (18)	25 (28)	0.09
Delayed CR (>28 days), *n* (%)	33 (27)	19 (21)	0.32
Median days from diagnosis to transplant (range)	175 (73–450)	164 (43–390)	0.44
Female to male	26 (25)	28 (34)	0.21
Donor–patient relation, *n* (%)			—
Father donor	36 (35)		
Mother donor	22 (21)		
Sibling donor	31 (30)	83 (100)	
Children donor	14 (14)		
HLA-A, B, DR, *n* (%)			—
3/6	69 (67)		
4/6	28 (27)		
5/6	6 (6)		
6/6		83 (100)	
Graft type, *n* (%)			
Bone marrow + peripheral blood cell	103 (100)	56 (62)	—
Bone marrow		6 (7)	
Peripheral blood cell		26 (31)	
Conditioning			—
TBI-based		21 (25)	
non-TBI	103 (100)	62 (75)	
Median nucleated cells, x10^8 cells/kg (range)	7.8 (4.5–16.9)	7.6 (4.0–17.7)	0.03
Median CD34$^+$ cells, x10^6/kg (range)	2.6 (0.8–7.7)	2.7 (0.6–6.8)	0.65
Median CD3$^+$ cells, x10^8 cells/kg (range)	1.2 (0.2–5.8)	1.7 (0.2–5.3)	<0.001

[a]Patient characteristics comparison is based on intent-to-treat analysis (total $n = 210$) while graft characteristics comparison is for patients finally transplanted (total $n = 186$).

[b]$\geq 30 \times 10^9$/L for B precursor ALL or $\geq 100 \times 10^9$/L for T-precursor ALL.

The 3-year DFS rate after HID-HSCT was similar to that after MSD-HSCT [68% (CI, 58–78) vs. 64% (CI, 52–76); $P = 0.56$; Fig. 3C]. No significant differences in OS [3-year rate, 75% (CI, 66–84) vs. 69% (CI, 58–80); $P = 0.51$; Fig. 3D] or NRM rates [3-year cumulative incidence, 13% (CI, 7–19) vs. 11% (CI, 4–18); $P = 0.84$, Fig. 3B] were observed after HID-HSCT and MSD-HSCT (Tables 2 and 3 and Figure 3). Patients receiving transplantations from maternal donors tended to have lower OS than those with other HIDs (60% vs. 80%, $P = 0.11$; Supplementary Fig. S1); in contrast, no differences in OS were found between HID-HSCT with 3/6 and 4–5/6 HLA matches (79% vs. 73%, $P = 0.65$; Supplementary Fig. S2). No differences in OS were found between MSD-HSCT with TBI-based regimen and non-TBI regimen (57% vs. 71%, $P = 0.22$), or between patients receiving BM or PBSCs and BM combined with PBSCs (50% vs. 73%, $P = 0.32$). Moreover, no significant influences of other factors, including patient age, patient–donor sex pair, and time to transplant, were identified in univariable (Supplementary Data) or multivariable analyses (Table 3). Increasing age (either as continuous variable or as each additional decade) was not significantly associated with a higher NRM or lower DFS; in addition, age younger than 30 years (treated as dichotomous variable, as referenced by Marks and colleagues; ref. 19) was not significantly associated with a higher NRM or lower DFS (Supplementary Data). The 3-year age-adjusted DFS rate after HID-HSCT was similar to that after MSD-HSCT [67% (CI, 58–77) vs. 65% (CI, 55–76); $P = 0.82$]. DFS between the three institutions were comparable when adjusted for pre- and post-transplant variables ($P = 0.42$; Table 3).

Among HID patients, the presence of cGVHD, especially the limited type, was found to be associated with lower relapse and better DFS and OS. CIR at 3-year for transplants without cGVHD tended to be higher than that for transplants with limited cGVHD (24% vs. 8%; $P = 0.11$). Transplants with limited chronic GVHD had better DFS (88%) than those with extensive cGVHD (57%, $P = 0.02$) or those without cGVHD (61%, $P = 0.02$). As with OS, transplants with extensive cGVHD (64%, $P = .032$) or those without cGVHD (70%, $P = 0.03$) had poorer OS than those with limited cGVHD (92%).

Discussion

To the best of our knowledge, this is the first prospective, multicenter study to compare HSCT from haploidentical with MSD HSCT in well-defined cohorts of adults with Ph-negative high-risk ALL in CR1 by using a standardized transplantation and prophylaxis protocol. Furthermore, the comparison provides a

Table 2. Outcomes after transplant according to donor source

Outcomes, % (95% CI)	Haploidentical ($N = 103$)	Matched sibling ($N = 83$)	P
Engraftment			
Neutrophil recovery at 30 d	99 (96–100)	98 (96–100)	0.19
Platelet recovery at 100 d	88 (82–94)	97 (94–100)	0.001
Time to sustained, days (range)			
Neutrophil > 0.5 × 10^9/L	12 (10–27)	13 (9–22)	
Platelet > 20 × 10^9/L	14 (7–72)	13 (8–38)	
Acute GVHD at 100 d			
Grades 2–4	28 (19–37)	13 (6–20)	0.008
Grades 3–4	6 (2–10)	2 (0–6)	0.25
Chronic GVHD at 3 y			
Limited + extensive	38 (29–47)	25 (15–35)	0.07
Extensive	14 (8–20)	8 (2–14)	0.21
Preemptive DLI, no.	5	5	
Full donor chimerism when DLI	5	4	
Relapse after DLI	2	1	
Relapse time after DLI, days	14, 82	100	
DFS after DLI	3	3	
DFS time after DLI, days	425,788,1329	292,1048,1075	
NRM after DLI	0	1 (584 days)	
Relapse, *n*	17	19	
Isolated bone marrow relapse	15/17	15/19	
Cumulative incidence at 3 y	18 (10–26)	24 (14–34)	0.30
Time to relapse, days (range)	188 (45–967)	330 (75–1129)	0.38
Therapy after relapse, *n*[a]	17	19	
Therapeutic DLI	12	7	
Full donor chimerism when DLI	10	5	
Sustained CR2 after DLI	6	4	
Sustained CR2 time, days	645 (317–1468)	540 (97–815)	
Death after DLI	6	3	
Death time after DLI, days	70 (58–73)	92, 140, 374	
No DLI after relapse	5	12	
Sustained CR2 achieved	0	1	
Sustained CR2 time	–	84	
Death	5	11	
Death time after relapse, days	50 (0–117)	69 (0–300)	
Non-relapse mortality at 3 y	13 (7–19)	11 (4–18)	0.84
DFS at 3 y	68 (58–78)	64 (52–76)	0.56
OS at 3 y	75 (66–84)	69 (58–80)	0.51
Follow-up in survivors, days	1,025 (370–1,638)	1,039 (380–1,623)	0.96

[a]In total, 10 of the 19 patients who underwent therapeutic DLI and 1 of the other 17 patients who did not undergo DLI achieved CR2 and are still alive ($P = 0.002$).

particular opportunity for exploring the up-to-date unestablished role of HID HSCT as post-remission therapy for high-risk ALL patients in CR1. Our study is the first to demonstrate that HID-HSCT is comparable with MSD-HSCT in the rate of DFS as post-remission treatment for this portion of patients, although the role of HID HSCT in the specific setting of ALL should be continuously evaluated on other HID approaches, such as post-transplantation cyclophosphamide (PTCY).

The 3-year NRM rate of 13% achieved in our HID patients was not only much lower than those reported in other myeloablative studies among HID patients (21–24), but also similar to that observed in studies of T-cell–replete HID HSCT using PTCY in non-myeloablative (NMA) settings (1-year NRM 8.7% vs. 7%; ref.25). Regarding GVHD, similar to our recently updated results (12, 26), the rates of GVHD observed after HID transplantation in our population were also comparable with those described in 80 patients who underwent G-CSF–primed BM transplantation from HIDs (24) as well as those described in 53 HID transplantations using PTCY reported by Bashey and colleagues (27). As for GVHD in MSD setting, our current results confirmed the finding from the Chinese Bone Marrow Transplant Cooperative Group (CBMTCG; refs.28 and29). Thus, the higher incidence of GVHD in the HID group is partly due to the relatively low incidence in the MSD cohort. On the other hand, the rates of both severe aGVHD and extensive cGVHD were comparable between the two groups.

In the current study, the CIR rate of 18% at 3-year in the HID group was somewhat lower than either those reported in other studies among HID patients (21–23) or that of 24% in patients who underwent MSD-HSCT in the present study. Modified DLI intervention guided by post-transplantation monitoring of MRD (16, 17) and potentially stronger GVL effect in HIDs transplant as compared with that from MSDs may be of value. In this analysis, we confirmed the beneficial effect of cGVHD on relapse by observing that there was a marked trend toward limited cGVHD being associated with less relapse and higher DFS among HID patients. It is of note that patients with adverse cytogenetics did not have a higher risk of relapse in this study. Similar findings after URD HSCT were previously reported (30). Furthermore, in our sibling donor cohort, the use of TBI did not result in superior outcomes as compared with non-TBI regimen (see Results). Although some studies demonstrated superior outcome using TBI as compared with BUCY after matched donor HSCT (31, 32), other reports did not find significant difference between TBI or non-TBI regimen for patients transplanted in CR (33, 34). Due to

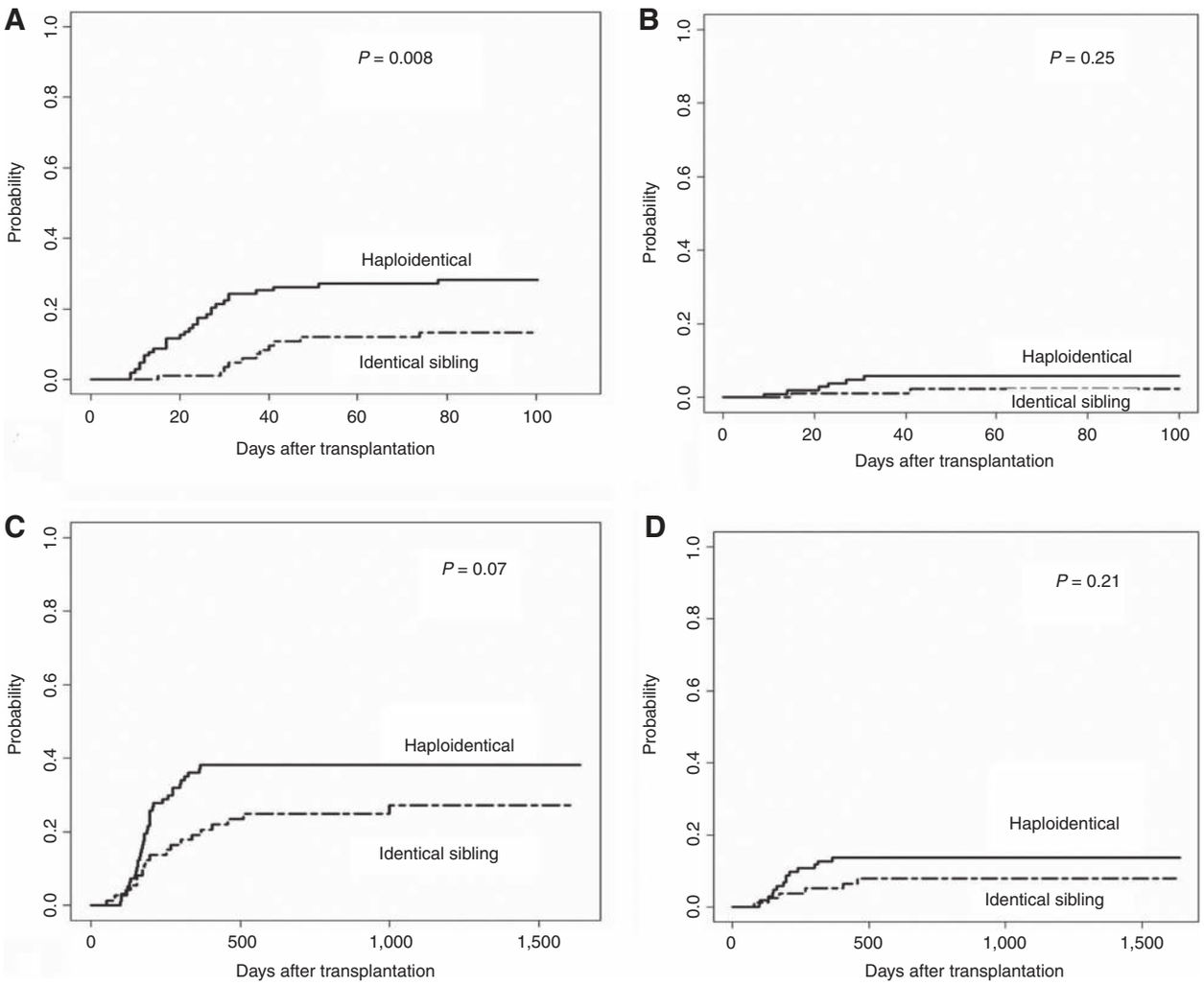

Figure 2.
GVHD after transplantation according to donor source. A, the incidence of acute GVHD of grades 2 to 4; B, the incidence of acute GVHD of grades 3 to 4; C, the incidence of chronic GVHD; D, the incidence of extensive chronic GVHD.

inconvenient TBI facilities and worry about the fertility, the uniform protocol (non-TBI) with our T-cell–replete modality was implemented in our haploidentical study population. TBI was only given to refractory/relapsed patients after our recent data showed comparable results with TBI or non-TBI conditioning (35).

Patient survival in this study was similar between the two study cohorts, but higher than those observed in other previous reports from HIDs transplant (21–23) due to a more favorable relapse rate and a much lower NRM. Several potential factors could account for our somewhat better outcomes for HIDs HSCT in comparison with those obtained by other studies. The first is the relative youth of our cohort, with particularly higher proportions of younger HID transplants (median age, 26 years; >35 years, 32%), although the median age of HID group was comparable with some other studies from HID (22, 23) or URD (14, 19) HSCT for patients with ALL in CR1. In other words, younger age in our study population is not the only contributing factor for better outcome, especially when compared with other reports with similar patient age. In addition, of interest is that in discordance with most studies (14, 19) but in keeping with some other studies (30), our data did not detect that older age was associated with lower survival. Therefore, this study provides evidence that HID HSCT can be safely applied to older individuals with Ph-negative ALL. Second, our patients actually had to survive for a median of nearly 6 months to receive MSD or HID transplant. This inherent bias is a possible cause of our good results. In some other studies, (DFS 38%–46%), median interval from CR1 to HID HSCT was 2–3 months (21, 24). This inherent selection bias may improve our outcomes, although the time to transplant was similar between our two study cohorts. Third, our good results may also be explained by the strategy for better estimates by post-HSCT MRD testing to stratify patients for risk of relapse and further MRD-guided individualization of therapy. However, one should be particularly cautious in interpreting the results, given the age difference between the two groups as it is known the biology of disease in older patients is different than in younger patients. Although overall survival is similar, a matched sibling transplant

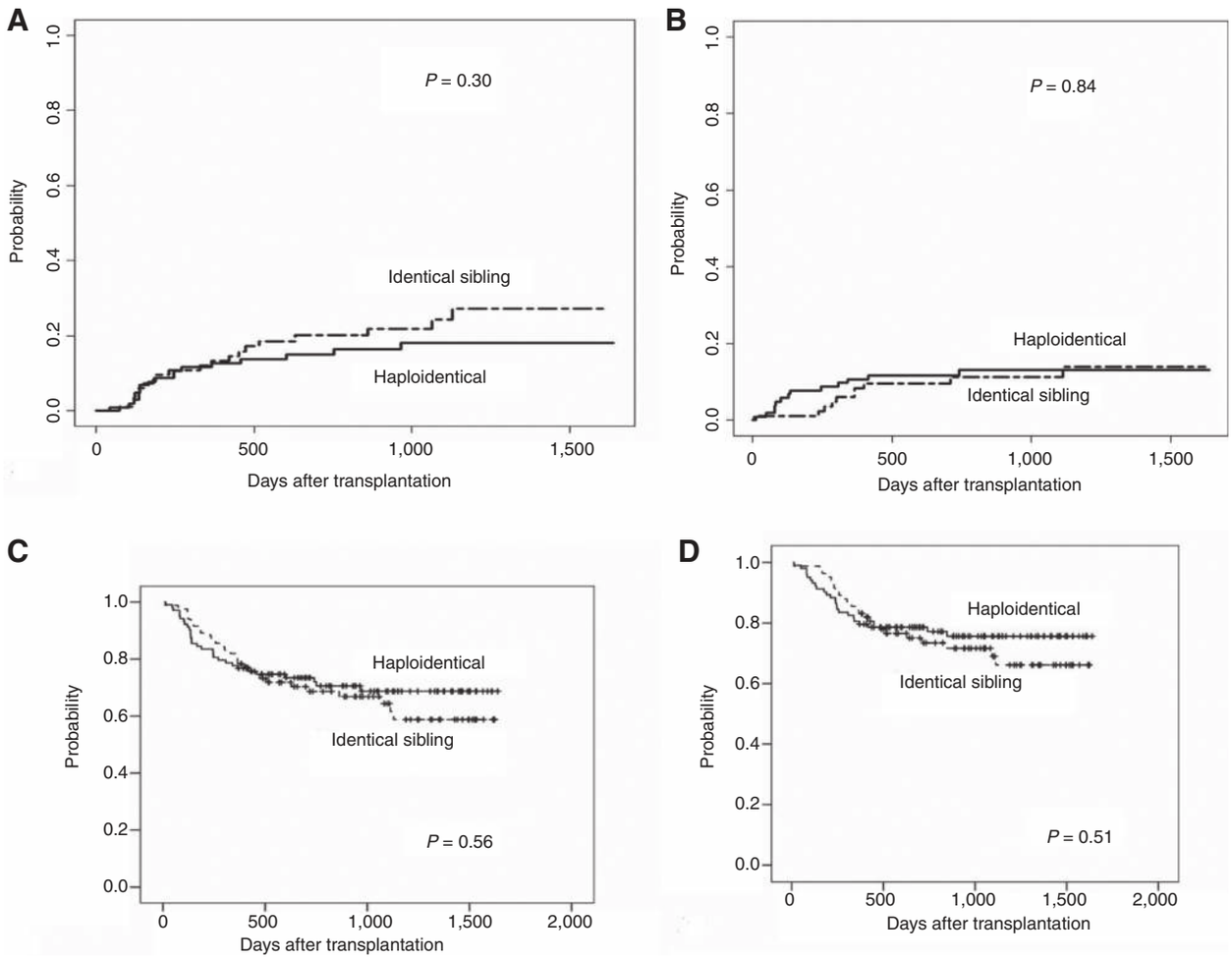

Figure 3.
Outcomes after transplantation according to donor source. A, the incidence of relapse; B, the incidence of non-relapse mortality; C, the rate of DFS; D, the rate of overall survival.

should still be considered the standard of care, compared with haploidentical transplants because it has lower toxicity (GVHD). In our study, no clear center effect was documented despite the unbalanced distribution of HSCT activity. Although patients receiving Haplo in Peking Unversity had better DFS ($P = 0.06$), we did not find any association of the center effect on haplo outcomes in multivariate analysis ($P = 0.37$, data not shown). This effect in univariate analysis might be due to the management of posttransplant complications, life-threatening infections, and relapse in each center. Importantly, transplant centers initiating haplo program need training and sharing of knowledge from experienced centers in helping to improve patient outcomes.

Some cautions in interpretation of the current data are important. First, the number of patients treated with allografts in ALL-CR1, although the largest HID transplant reported for the specific, homogenous population, is still relatively small. Nonetheless, one should consider the prospective nature of this study, and the size of our study population was quite impressive in 3.5-year recruitment period when compared with those in other studies (comparable size during 9–14 years using URD or MSD; refs.14 and 19). In addition, insufficient confidence in HID transplant resulted in less HID transplant (maybe more patients with very high-risk features were tended to be "selected" into HID group as a result) than the number could be, although consecutive patients entering either transplant group were analyzed. Second, given the biologic randomization, patients were stratified for known risks. For instance, the MSD group had twice as many over age 35; further, the graft source and the conditioning differed between the two groups for some reason mentioned above. Despite our effort on adjustments, the possible influence of the imbalanced factors on comparable outcomes between these study cohorts cannot be eliminated completely. Third, insufficient data on pre- and post-transplant MRD in all participating centers, co-morbidities, and natural killer (NK) cell allo-reactivity limit our ability to incorporate these important variables into analysis.

Our data demonstrate excellent DFS and OS, and low incidence of relapse in adults with Ph-negative high-risk ALL in CR1 from HLA-matched siblings or HIDs and outcomes are similar between the two cohorts. As demonstrated in our recently published report, outcomes after transplantation using HIDs are comparable

Table 3. Results of multivariate analysis of outcomes after transplant

Outcome	Hazard ratio (95% CI)	*P*
DFS		
Haploidentical vs. matched sibling	0.95 (0.48–1.89)	0.88
Patient age <30 vs. >30 years	0.74 (0.42–1.28)	0.28
Patient sex male vs. female	1.08 (0.53–2.18)	0.83
Time to transplant <6 vs. >6 months	1.48 (0.86–2.56)	0.16
Female-to-male vs. other sex pair	1.03 (0.56–1.89)	0.91
Limited chronic GVHD vs. no or extended	0.59 (0.29–1.17)	0.13
Total body irradiation, no vs. yes	1.16 (0.45–2.97)	0.75
Bone marrow or peripheral blood vs. both	0.80 (0.32–1.98)	0.63
Transplant center		0.42
Peking University	1.0	–
Southern Medical University	1.26 (0.47–3.33)	0.63
Soochow University	1.55 (0.80–2.99)	0.19
OS		
Haploidentical vs. matched sibling	0.91 (0.50–1.70)	0.77
Patient age <30 vs. >30 years	0.60 (0.33–1.11)	0.11
Patient sex male vs. female	1.13 (0.55–2.30)	0.74
Time to transplant <6 vs. >6 months	1.64 (0.89–3.01)	0.11
Female-to-male vs. other sex pair	1.22 (0.64–2.31)	0.54
Limited chronic GVHD vs. no or extended	0.59 (0.27–1.28)	0.18
Relapse		
Haploidentical vs. matched sibling	0.67 (0.33–1.36)	0.27
Patient age <30 vs. >30 years	1.06 (0.50–2.28)	0.87
Patient sex male vs. female	1.52 (0.64–3.62)	0.35
Time to transplant <6 vs. >6 months	1.42 (0.69–2.90)	0.33
Female-to-male vs. other sex pair	0.61 (0.26–1.45)	0.27
Limited chronic GVHD vs. no or extended	0.65 (0.26–1.62)	0.36
Non-Relapse-Mortality		
Haploidentical vs. matched sibling	1.38 (0.58–3.35)	0.46
Patient age <30 vs. >30 years	0.47 (0.19–1.17)	0.11
Patient sex male vs. female	0.66 (0.19–2.33)	0.52
Time to transplant <6 vs. >6 months	1.66 (0.70–3.92)	0.25
Female-to-male vs. other sex pair	1.53 (0.64–3.69)	0.34
Limited chronic GVHD vs. no or extended	0.63 (0.21–1.86)	0.40

with those after MSDs transplantation for intermediate- or high-risk AML patients in CR1 (12), the application of haploidentical HSCT in ALL need to be broadened (27, 36). All the more, our observations provide evidence to support the rationale for considering haploidentical HSCT as a first-line post-remission treatment option for adults with high-risk ALL who lack a matched donor; careful validation of other available HID strategies, such as PTCY, is required to define further the role of HID HSCT in this disease.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): Y. Wang, X.-J. Huang
Writing, review, and/or revision of the manuscript: Y. Wang, D.-P. Wu, X.-J. Huang
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): X.-J. Huang
Study supervision: X.-J. Huang

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