Haploidentical vs identical-sibling transplant for AML in remission: a multicenter, prospective study

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Key Points
• Haploidentical transplant achieves outcomes similar to those of identical-sibling transplant for AML patients in first remission.
• Haploidentical transplant is a valid postremission treatment of intermediate- or high-risk AML patients lacking an identical donor.

AML patients in CR1. Such transplantation was demonstrated to be a valid alternative as postremission treatment of intermediate- or high-risk AML patients lacking an identical donor. This trial was registered at www.chictr.org as #ChiCTR-OCH-10000940. (Blood. 2015;125(25):3956-3962)

Introduction

Acute myeloid leukemia (AML) is a common hematologic malignant disease. HLA-identical sibling donor (ISD) hematopoietic stem cell transplantation (HSCT) offers significantly improved overall survival (OS) for intermediate- or high-risk AML patients compared with chemotherapy alone1-5; thus, it is recommended as a first-line postremission treatment in this clinical situation. Recent progress in haploidentical donor (HID) transplantation provides the benefits of rapid and near-universal donor availability.6-8 However, whether haploidentical HSCT could serve as a first-line postremission therapy in intermediate- or high-risk AML remains to be determined.

In recent years, our group established an unmanipulated haploidentical blood and marrow transplantation protocol in which anti-thymocyte globulin (ATG) in the conditioning and the powerful posttransplantation graft-versus-host disease (GVHD) prophylaxis probably provided a major contribution to controlling alloreactivity.7,8 Additionally, our recent single-institute, patient self-selected study showed that haploidentical HSCT was superior to chemotherapy alone for patients with intermediate- or high-risk AML in the first complete remission (CR1).9 Undoubtedly, randomized trials are needed to determine if haploidentical transplantation is, in fact, superior to chemotherapy for AML in CR1. However, this may be difficult to determine in this setting because of ethical and practical reasons given the inferior outcomes observed after chemotherapy-based postremission strategies compared with those after allo-HSCT.1,3-5 Conversely, prior single-center analyses demonstrated similar survival after unmanipulated HID HSCT using ATG vs ISD HSCT for hematologic malignancies.10,11 Taken together, we hypothesized that haploidentical HSCT is a valid option as a postremission treatment of AML in CR1. The results from haploidentical HSCT have not formally been compared in prospective studies with those from ISDs to evaluate the value of haploidentical HSCT for the specific, homogenous disease of intermediate- or high-risk AML in CR1. In addition, evaluating a uniform haplo-HSCT protocol in more clinical centers would enable prospective, multicenter trials on the standardized treatment. Therefore, based on the current prospective, multicenter, disease-specific study, we compare the outcomes of consecutive AML patients in CR1 undergoing T-cell–replete haploidentical HSCT uniformly performed at 3 centers with all contemporary ISD HSCT.

The effects of HLA-identical sibling donor (ISD) hematopoietic stem cell transplantation (HSCT) on adults with intermediate- or high-risk acute myeloid leukemia (AML) in the first complete remission (CR1) are well established. Previous single-center studies have demonstrated similar survival after unmanipulated haploidentical donor (HID) vs ISD HSCT for hematologic malignancies. To test the hypothesis that haploidentical HSCT would be a valid option as postremission therapy for AML patients in CR1 lacking a matched donor, we designed a disease-specific, prospective, multicenter study. Between July 2010 and November 2013, 450 patients were assigned to undergo HID (231 patients) or ISD HSCT (219 patients) according to donor availability. Among HID and ISD recipients, the 3-year disease-free survival rate was 74% and 78% (P = .34), respectively; the overall survival rate was 79% and 82% (P = .36), respectively; cumulative incidences of relapse were 15% and 15% (P = .88); and those of the nonrelapse-mortality were 13% and 8% (P = .13), respectively. In conclusion, unmanipulated haploidentical HSCT achieves outcomes similar to those of ISD HSCT for AML patients in CR1 lacking a matched donor. This trial was registered at www.chictr.org as #ChiCTR-OCH-10000940. (Blood. 2015;125(25):3956-3962)

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Median CD34 and inv(16) or t(16;16)(p13;q22) were considered low risk. Complex cytogenetic abnormalities. Cytogenetic abnormalities t(8;21)(q22;q22), t(15;17)(q22;q21), screening for fusion genes was offered to all patients. Patients were classified as low, Follow-up time in survivors from

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Haploidentical, N = 231</th>
<th>Identical sibling, N = 219</th>
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<tr>
<td>Age, y, median (range)</td>
<td>28 (15-57)</td>
<td>40 (17-60)</td>
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<td>Gender, no. (%)</td>
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<td>Female 87 (38) 97 (44)</td>
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<tr>
<td>French-American-British subtype, no. (%)</td>
<td>M0 5 (2) 6 (3)</td>
<td>M1 11 (5) 23 (10)</td>
</tr>
</tbody>
</table>
| WBC count at diagnosis (range; 365-1612 days) after HSCT. This article focuses on the primary end points. Analyses of immune reconstitution are ongoing. Patients

| Study design

We conducted a disease-specific, multicenter, nonrandomized trial. Patients were assigned to undergo haploidentical or ISD HSCT according to donor availability. The primary end point was disease-free survival (DFS), OS, and relapse rates. Secondary end points included an evaluation of immunologic reconstitution. Enrollment began in July 2010 and ended after the accrual goal was met, which occurred in November 2013. The analysis includes data collected as of November 30, 2014. The median follow-up for surviving patients is 952 days (range: 365-1612 days) after HSCT. This article focuses on the primary end points. Analyses of immune reconstitution are ongoing.

| Patients

Eligible patients were aged 15 to 60 years and had intermediate- or high-risk AML in CR1 with no contraindications to HSCT. HLA-ISD was the first choice for allotransplantation. If an HLA-ISD was unavailable, subjects without a suitable closely HLA-matched unrelated donor (>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-haploptotype transplantation. Consecutive patients receiving HID (n = 231) or ISD (n = 219) HSCT during the study period were enrolled. For this comparative analysis to arrive at comparable patient cohorts that received transplants during the same time interval, we excluded patients who received unrelated donor HSCT (n = 58).

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 enrollment. All authors vouch for the accuracy and completeness of the reported data and analyses and for the adherence of the study to the protocol. This study was registered as ChICTR-OCCH-10000940 at www.chictr.org.

| Procedures

Patients were classified as intermediate- or high-risk based on National Comprehensive Cancer Network cytogenetic abnormalities. Information on the monoclonal karyotype,14 Center for International Blood and Marrow Transplant registry.

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GVHD prophylaxis regimen consisted of cyclosporine A, mycophenolate mofetil, and short-term methotrexate. Between May 2012 and November 2013, 25 subjects in Peking University were randomized to receive low-dose corticosteroid prophylaxis (www.clinicaltrials.gov, #NCT01607580). After completion of the study treatment, BM 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. In Peking University, modified donor lymphocyte infusion (DLI) would be given before hematologic relapse as the intervention therapy (preemptive DLI) after 3 months post-HSCT following a trial of immunosuppressant withdrawal. The detailed criteria for preemptive DLI administration included the following: (1) patients scored as MRD+ if they had 2 consecutive positive results using flow cytometry or Wilms’ tumor gene 1 or were both flow cytometry–positive and Wilms’ tumor gene 1–positive in a single sample within 1 year after transplantation; (2) no uncontrolled GVHD or life-threatening infection; and (3) with donor availability and willingness. Patients with GVHD first received GVHD therapy. After GVHD was controlled, MRD testing was repeated, and those patients that remained MRD+ received modified DLI. In total, 23 patients (13 HID, 10 ISD) required this preemptive approach, which occurred at a median of 171 days (range, 109-319 days) after transplantation. The modified DLI regimen was as previously described. When a hematologic relapse was diagnosed after HSCT, posttransplant 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 PB stem cell collection again, the patients would receive chemotherapy alone. Antileukemia chemotherapy before DLI included aclacinomycin (10 mg/m² per day for 5 days) and Ara-C (100 mg/m² per day for 5 days); fludarabine (30 mg/m² per day for 5 days), Ara-C (1.0 g every 12 hours for 10 doses), and G-CSF; or harringtonine (2 mg/m² per day for 5 days), aclacinomycin (10 mg/m² per day for 5 days), and Ara-C (100 mg/m² per day for 5 days). In total, 18 patients (11 HID, 7 ISD) were given this targeted therapeutic DLI (see “Results”). The median number of CD3⁺ cells infused in each patient was 0.58 (interquartile range, 0.13–2.03) × 10³/kg. Chimerism analyses were done by DNA fingerprinting of short tandem repeat on blood samples.

Statistical analysis

Comparisons of patient characteristics between the 2 groups were performed using the Mann-Whitney U test for continuous variable and χ² test for categorical data. Relapse, nonrelapse mortality (NRM), engraftment, and GVHD were estimated as cumulative incidences, taking into account competing risks. NRM was defined as death from any cause in the first 28 days post-HSCT or death without evidence of disease recurrence beyond day 28. Relapse was defined as recurrence of BM blasts >5%, reappearance of blasts in the blood, or development of extramedullary disease infiltrates at any site. Assessments of engraftment and chimerism were previously described in detail. 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 was evaluated and graded by a single practitioner within the program.

Survival functions were estimated using the Kaplan-Meier method and compared by the log-rank test. The starting point for comparing outcomes between the cohorts was the point when complete remission was declared. Univariate probabilities of survival and DFS were calculated using a left-truncated version of the Kaplan-Meier estimator with 95% confidence intervals.
Cumulative incidence of relapse (CIR) and NRM were calculated using a left-truncated version of cumulative incidence function to accommodate competing risks. To adjust for the differences in baseline characteristics, left-truncated versions of the 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 ISD, using ISD as the reference group) into the models. Backward elimination with a criterion of $P < .10$ for retention was used to select a final model. The following variables were analyzed: patient age ($\geq 50$ years or not), sex (female or male), WBC count at diagnosis ($> 50 \times 10^9/L$ or not), cytogenetic risk group (intermediate or high), and courses to achieving CR1 ($\geq 2$ courses or not). The assumption of proportional hazards for each factor in the Cox model was tested. The test indicated that the proportionality assumptions hold. End-point events for DFS included morphologic relapse and NRM in CR1. Patients with MRD were not considered relapsed for DFS determination. Since conventional measures of leukemia-free survival (LFS) fail to take into account the capacity of DLI to produce durable molecular remissions in patients who relapse, thus underestimating the ability of allografting to produce sustained DFS even in patients who have relapsed, the current LFS probabilities were also estimated.20 The SAS V. 9.3 (SAS Institute Inc., Cary, NC) and SPSS 13.0 software packages (SPSS Inc., Chicago, IL) were used for data analyses.

**Results**

**Patient characteristics**

As shown in Table 1, the groups were well matched, except that patients undergoing HID-HSCT were significantly younger and there was a little delay from diagnosis to transplantation. Because of the 1-child policy in China over the past 30 years, parent donors accounted for 50% of the HID group. As a result, the HID cohort was younger. The phenomenon of 1 month longer to transplant in the HID vs the ISD group may be explained by the possible hesitation of patients, which is associated with unawareness arising from a lack of a doctor’s referral during chemotherapy in small institutes or insufficient confidence in HID transplantation. Patients undergoing HSCT using HIDs were mismatched at a median of 3 of 6 HLA-A, B, and DRB1 loci by molecular typing (range, 1-3).

**Survival**

The 3-year probabilities of DFS were 74% (95% CI, 67-81) and 78% (95% CI, 72-85; $P = .34$) among HID and ISD patients (Figure 1A). The 3-year probabilities of current LFS were 76% (95% CI, 64-87) and 80% (95% CI, 70-91) among HID and ISD patients. The 3-year probabilities of OS were 79% (95% CI, 73-85) and 82% (95% CI, 76-88; $P = .36$) among HID and ISD patients (Figure 1B). The 3-year cumulative incidences of NRM were 13% (95% CI, 7-19) and 8% (95% CI, 4-12; $P = .13$; Figure 1C). Subgroup analysis with available FLT-ITD results at diagnosis showed that the 3-year DFS rates were 79% (95% CI, 71-88) and 60% (95% CI, 42-78) among patients without FLT-ITD and patients with FLT-ITD ($P = .02$).

Univariate analysis treated the patient age in different ways: (1) as a continuous variable; and (2) in addition, a dichotomous variable of 50 years old was used as reported by Yanada et al19 for matched donor transplant. Univariate analysis showed that patient age did not affect
DFS as a continuous variable \((P = .39)\), whereas patient age over 50 years old significantly affected DFS \((P = .03)\). This is likely because of the significantly higher proportion of WBC count at diagnosis as well as higher proportion of cytogenetically high-risk patients within the older group as compared with that in the younger group \((45\% \text{ vs } 26\%, P = .01; 30\% \text{ vs } 17\%, P = .03, \text{ respectively})\). Of note, however, the differences in DFS rates between age groups differed according to donor source. DFS was not significantly different for patients over 50 years or not \((62\% \text{ vs } 75\%, P = .37)\) in the HID cohort, whereas DFS was significantly lower among those over 50 years than those under 50 years \((61\% \text{ vs } 81\%, P = .02)\) in the ISD group. The previously mentioned different proportion of disease characteristics and the more prominent differences within the ISD group are likely to have contributed to differences in DFS between the 2 age groups. In addition, the effect of patient age on DFS disappeared in multivariate analysis \((P = .11)\).

A multivariate analysis failed to show significant differences in DFS, OS, or NRM rates between the 2 cohorts; cytogenetic risk group and WBC count at diagnosis were independent risk factors associated with DFS and OS, and patient age, sex, or courses required to achieving CR1 did not significantly affect mortality \((P = .11)\).

### Relapse

The 3-year CIRs were 15% \((95\% \text{ CI}, 9-21)\) and 15% \((95\% \text{ CI}, 9-21; P = .98)\) among HID and ISD patients \((Figure \text{ 1D})\). Multivariate analysis failed to show significant differences in CIR between the 2 cohorts; cytogenetic risk group and WBC count at diagnosis were independent risk factors affecting CIR \((P = .11)\).

At Peking University, full donor chimerism was detected in 22 of the 23 \((96\%)\) patients at the time of preempotive DLI. Among the 23 patients \((13 \text{ HID, } 10 \text{ ISD})\) receiving modified DLI as intervention for positive MRD, 7 \((4 \text{ of } 13 \text{ HID and } 3 \text{ of } 10 \text{ ISD})\) eventually relapsed at a median of 194 days \((range, 85-780 \text{ days})\) after DLI, and 15 patients were alive without relapse with a median of 940 days \((range, 214-1349 \text{ days})\) after DLI; the remaining 1 patient died of infection.

Until the last follow-up, 26 and 27 patients experienced relapse after HID- or ISD-HSCT; of the 26 HID patients, 11 received DLI plus chemotherapy, 10 received chemotherapy alone, and 5 received no further therapy. In the DLI plus chemotherapy group, 6 patients achieved the second complete remission \((CR2)\) and are still alive with a median of 323 days after relapse, whereas 3 died of relapse \((76, 209, \text{ and } 397 \text{ days after DLI})\) and the other 2 died of infection. The patients who received chemotherapy alone or no therapy died at a median of 60 days after relapse. Among ISD patients, 27 experienced relapse; of these, 7 received DLI plus chemotherapy, 8 received chemotherapy alone, and 12 received no further therapy. In the DLI plus chemotherapy group, 4 patients achieved CR2 and are still alive with a median of 844 days after relapse, whereas 3 died of relapse \((30, 146, \text{ and } 185 \text{ days after DLI})\). Among the 8 patients who received chemotherapy alone, 2 patients achieved CR2 and are still alive \((94 \text{ and } 194 \text{ days after relapse})\) and 6 died at a median of 36 days after relapse. Although the 12 patients receiving no further therapy died at a median of 30 days after relapse. In total, 10 of the 18 patients who underwent therapeutic DLI and 2 of the other 35 patients who did not undergo DLI achieved CR2 and are still alive \((P < .001)\). Full donor chimerism was detected in 14 of the 18 \((80\%)\) patients at the time of targeted therapeutic DLI. The 1-year CIR after preemptive DLI or targeted therapeutic DLI was 22% and 33% \((P = .42)\), respectively.

### Engraftment and GVHD

All patients achieved donor-cell engraftment. The median time to achieve neutrophil engraftment was 2 days shorter \((P = .004; \text{ Figure 1E})\) after HID-HSCT, whereas that of platelet engraftment was 3 days shorter after ISD-HSCT \((P < .001; \text{ Figure 1F})\).

The cumulative incidences of grades 2 to 4 acute GVHD at 100 days were 36% \((95\% \text{ CI}, 30-42)\) and 13% \((95\% \text{ CI}, 9-17)\) after HID- or ISD-HSCT, respectively \((P < .001; \text{ Figure 1G})\); the cumulative incidences for grades 3 to 4 acute GVHD at 100 days were 10% \((95\% \text{ CI, 6-14})\) and 3% \((95\% \text{ CI, 1-5})\), respectively \((P = .004)\). The cumulative incidences of chronic GVHD at 1 year were 42% \((95\% \text{ CI, 36-48})\) vs 15% \((95\% \text{ CI, 10-20})\) for HID vs ISD patients \((P < .001; \text{ Figure 1H})\); the cumulative rates of severe chronic GVHD at 1 year were 12% \((95\% \text{ CI, 8-16})\) and 2% \((95\% \text{ CI, 0-4})\), respectively \((P < .001)\).

### Discussion

To our knowledge, our study represents the first formal comparison of HID transplantation with allo-HSCT using ISDs in a disease-specific population of patients with intermediate- or high-risk AML in CR1. Although the study was nonrandomized, its strengths include the prospective nature, uniform treatment modality at the multiple centers, contemporaneous population of patients studied, and the number of patients analyzed. Furthermore, the comparison provides a particular opportunity for exploring the up-to-date undefined role of HID HSCT as postremission therapy for intermediate- or high-risk AML patients in CR1. Our study is the first to demonstrate that HID-HSCT is comparable to ISD-HSCT in the rate of DFS as postremission treatment of this portion of patients and the rates of OS and relapse were also similar in the 2 groups.

In our analysis, a 1.5-year NRM rate of 10% was achieved in the HID patients, which is comparable with the low 1-year NRM of 7% observed in studies of T-cell–replete HID HSCT using posttransplantation cyclophosphamide in nonmyeloablative settings.\(^{21}\) Our analysis demonstrates that low rates of NRM can be achieved among AML patients in CR1 undergoing both HID and ISD transplantation performed in multi-institutions. Nonetheless, both groups are relatively young, and this may have contributed to reduce the severity of NRM. It should also be noted that NRM was substantially higher with haploidentical transplants compared with those with matched related donors, although it did not reach statistical significance. Regarding GVHD, similar to our recently updated results,\(^{22}\) the rates of GVHD observed

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**Table 2. Results of multivariate analysis of outcomes and contributing factors**

<table>
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<tr>
<th>Outcome</th>
<th>Hazard ratio (95% CI)</th>
<th>(P)</th>
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</thead>
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<td>DFS</td>
<td></td>
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<tr>
<td>Identical sibling vs haploidentical</td>
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<td>Other significant factors</td>
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<td>Cytogenetic risk high vs intermediate</td>
<td>1.93 (1.18-3.15)</td>
<td>.008</td>
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<tr>
<td>WBC &gt;50 000 vs &lt;50 000 per mm(^3)</td>
<td>1.92 (1.21-3.04)</td>
<td>.005</td>
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<tr>
<td>OS</td>
<td></td>
<td></td>
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<tr>
<td>Identical sibling vs haploidentical</td>
<td>0.80 (0.47-1.37)</td>
<td>.43</td>
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<tr>
<td>Other significant factors</td>
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<td>Cytogenetic risk high vs intermediate</td>
<td>0.62 (0.36-1.06)</td>
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<tr>
<td>WBC &gt;50 000 vs &lt;50 000 per mm(^3)</td>
<td>0.51 (0.31-0.83)</td>
<td>.007</td>
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<tr>
<td>NRM</td>
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<tr>
<td>Identical sibling vs haploidentical</td>
<td>1.06 (0.58-1.92)</td>
<td>.85</td>
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<tr>
<td>Other significant factors</td>
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<tr>
<td>Cytogenetic risk high vs intermediate</td>
<td>1.88 (1.05-3.76)</td>
<td>.04</td>
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<tr>
<td>WBC &gt;50 000 vs &lt;50 000 per mm(^3)</td>
<td>2.15 (1.18-3.91)</td>
<td>.01</td>
</tr>
</tbody>
</table>

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after HID transplantation in our population were also comparable to those described in 53 HID transplantations using posttransplantation cyclophosphamide reported by Bashey et al. However, the rates of GVHD observed after ISD transplantation in our population were much lower than those after nonmyeloablative ISD transplant described in Bashey’s report. Recently, a multicenter phase 2 study from the Chinese Bone Marrow Transplant Cooperative Group showed that a combination of cyclosporine A, methotrexate, and mycophenolate mofetil for GVHD prophylaxis significantly decreased the risk of acute GVHD compared with historical controls in ISD transplantation. This finding is confirmed in our ISD cohort. Thus, the higher incidence of GVHD in the HID group is partly because of the relatively low incidence in the ISD cohort. Furthermore, the GVHD rates in HID group were quite acceptable as discussed previously and the rates of GVHD-related death were similar between the two groups (data not shown) because of effective therapy. The CIR of 15% at 3 years in the HID group was similar to that of 12% reported in our previous study and to patients who underwent ISD-HSCT in the present study but lower than those reported in other studies. Posttransplantation monitoring of MRD and modified DLI intervention guided by MRD level might have further decreased the relapse rate.

Survival should be the primary end point for assessing the efficacy of a treatment modality for leukemia. Patient survival in this study was similar to that of our own previous study, but higher than that observed in other previous reports because of a more favorable relapse rate and a much lower NRM. Several factors likely contributed to our superior transplantation outcomes. First, the patients in other haploidentical report or 50 years old in ISD transplant), our present study than in other studies (median age of 28 vs 33 to 37 in other study population. Second, as mentioned previously, younger age in HID group is partly because of the relatively low incidence in the ISD cohort. Furthermore, the GVHD rates in HID group were quite acceptable as discussed previously and the rates of GVHD-related death were similar between the two groups (data not shown) because of effective therapy. The CIR of 15% at 3 years in the HID group was similar to that of 12% reported in our previous study and to patients who underwent ISD-HSCT in the present study but lower than those reported in other studies. Posttransplantation monitoring of MRD and modified DLI intervention guided by MRD level might have further decreased the relapse rate.

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Haploidentical vs identical-sibling transplant for AML in remission: a multicenter, prospective study

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