Myeloablative Haploidentical Transplantation Is Superior to Chemotherapy for Patients with Intermediate-risk Acute Myelogenous Leukemia in First Complete Remission

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Abstract

Purpose: Although myeloablative HLA haploidentical hematopoietic stem cell transplantation (haplo-HSCT) following pretransplant anti-thymocyte globulin (ATG) and granulocyte colony-stimulating factor (G-CSF) stimulated grafts (ATG+G-CSF) has been confirmed as an alternative to HSCT from HLA-matched sibling donors (MSD), the effect of haplo-HSCT on postremission treatment of patients with acute myeloid leukemia (AML) with intermediate risk (int-risk AML) who achieved first complete remission (CR1) has not been defined.

Patients and Methods: In this prospective trial, among 443 consecutive patients ages 16–60 years with newly diagnosed de novo AML with int-risk cytogenetics, 147 patients with molecular int-risk AML who achieved CR1 within two courses of induction and remained in CR1 at 4 months postremission either received chemotherapy (n = 69) or underwent haplo-HSCT (n = 78).

Results: The 3-year leukemia-free survival (LFS) and overall survival (OS) were significantly higher in the haplo-HSCT group than in the chemotherapy group (74.3% vs. 47.3%; P = 0.0004 and 80.8% vs. 53.5%; P = 0.0001, respectively). In the multivariate analysis with propensity score adjustment, postremission treatment (haplo-HSCT vs. chemotherapy) was an independent risk factor affecting the LFS [HR 0.360; 95% confidence interval (CI), 0.163–0.793; P = 0.011], OS (HR 0.361; 95% CI, 0.156–0.832; P = 0.017), and cumulative incidence of relapse (HR 0.161; 95% CI, 0.057–0.459; P = 0.001) either in entire cohort or stratified by minimal residual disease after the second consolidation.


Introduction

Intermediate risk (int-risk) acute myeloid leukemia (AML) represents a heterogeneous, continuously evolving group of diseases based on the MRC/SWOG/NCCN/ELN criteria. It is estimated that approximately 37%–42% of AMLs fall into the int-risk category. The outcome for these patients remains unsatisfactory, as evidenced by a 3- to 5-year cumulative incidence of relapse (CIR) and overall survival (OS) rates of 45%–53% and 34%–41%, respectively (1–3).

Allogeneic hematopoietic stem cell transplantation (allo-HSCT), especially from HLA-matched sibling donors (MSD) or matched unrelated donors (MUD), is one of the standard options and possibly the preferred option for individuals with int-risk AML (6–10). Although emerging data suggest that MSD-HSCT or MUD-HSCT may be superior to chemotherapy alone for the management of int-risk AML (10–12), the shortage of MSDs and limited availability of MUDs (especially in non-Caucasian populations) prevents large populations from benefiting from allo-HSCT (13–16).

Recently, haploidentical HSCT (haplo-HSCT) was confirmed as an equally good alternative to MSD-HSCT as a postremission therapy for patients with AML in the first morphologic complete remission (CR1) who lack a matching donor. Specifically, haplo-HSCT with a posttransplant cyclophosphamide (PT-CY) protocol (established by a Baltimore group) or pretransplant
Translational Relevance

Acute myeloid leukemia with intermediate risk (cytogenetic and molecular; int-risk AML) accounts for 37%–42% of all AML cases. Haploidentical family donors provide excellent donor availability and participate in more than 15%–18% of allogeneic–hematopoietic stem cell transplantation (HSCT) procedures in Europe and the United States and 56.4% in China. The results of this trial will help answer the question of whether patients with int-risk AML who are in first complete remission should search for haplo donors and undergo haploidentical HSCT instead of consolidation chemotherapy in the absence of matched sibling donors or matched unrelated donors.

Available data suggest that haplo-HSCT is a feasible treatment option for patients with int-risk AML who lack an HLA-matched donor, but limited data are available to compare the efficacy of haplo-HSCT and chemotherapy. Therefore, it is unknown whether this patient subset should search for a haplo donor in CR1 and pursue haplo-HSCT instead of consolidation chemotherapy in the absence of MSDs and MUDs (6, 18, 31). To address this question, Huang and colleagues suggested that myeloablative haplo-HSCT with ATG+G-CSF may be superior to chemotherapy as a postremission treatment for individuals with int-risk or high-risk cytogenetic AML in CR1, as indicated by the lower CIR (12.0% vs. 57.8%; P < 0.0001) and improved 3-year LFS (73.1% vs. 44.2%; P < 0.0001; ref. 32). However, no subgroup data for int-risk AML in CR1 are available from this previous study, especially considering the incomplete data on molecular markers such as nucleophosmin 1 (NPM1) and FMS-like tyrosine kinase 3 internal tandem duplication (FLT3-ITD). In addition, the impact of imbalanced patient characteristics, such as the lower median age in the haplo-HSCT cohort than in the chemotherapy group, likely affected the observed outcomes. Thus, whether the benefit of haplo-HSCT in individuals with heterogeneous AML can be replicated for those with int-risk AML remains controversial (31, 33).

We hypothesized that compared with chemotherapy, myeloablative haplo-HSCT with ATG+G-CSF as a postremission treatment in patients with int-risk AML will have a favorable impact on survival in a prospective clinical study. This trial was registered at the Chinese Clinical Trial Registry (ChiCTR-OCH-10000940).

Patients and Methods

Patients

Newly diagnosed patients with AML were enrolled in this study from June 2010 to December 2014. Patients met the following inclusion criteria: age between 15 and 60 years; intermediate AML based on National Comprehensive Cancer Network (NCCN) 2009, which excludes the favorable abnormalities t(8;21)(q22; q22), t(15;17)(q22;q21), and inv(16) or t(16;16)(p13;q22); NPM1+FLT3-ITD- and adverse-risk abnormalities; complex cytogenetic abnormalities (defined as at least three unrelated cytogenetic clones); monosomal karyotype; 5/5q; 7/7q; inv(3) (q21.3;q26.2)/t(3:3)(q23.3;q26.2); t(6;9)(q23;q34); abn11(q23)-none t(9;11), t(9;22)(q34;q11); the FLT3-ITD mutation; and CR, which includes CR [absolute neutrophil count (ANC) ≥ 1 x 10⁹/L and platelet (PLT) count ≥ 100 x 10⁹/L], CR with incomplete PLT recovery (CRp) or CR with incomplete ANC and PLT recovery (CRI; ref. 4); and physical score (ECOG) 0–2, with hematopoietic cell transplantation-specific comorbidity index (HCT-CL) 0–2 (34, 35) at baseline with no contraindications to consolidation or HSCT. Donor searches for MSDs, MUDs, or haplo MSDs were initiated during induction. The first choice was MSD-HSCT after two cycles of consolidation. If an MSD was unavailable, subjects without a suitable MUD were adequately informed by their physician about the latest results of evidence-based studies and recommendations from guidelines. Patients who met the recruitment criteria after the second consolidation underwent full discussions with doctors and then made decisions on their own intention to receive haplo-HSCT. For each patient, informed consent was obtained from patients or guardians in accordance with the Declaration of Helsinki. The trial was approved by the ethical committee at Peking University People’s Hospital (Beijing, China). Figure 1 provides an overview of the enrolled patients, including risk classification, HLA typing, and donor availability.

Diagnoses and assessment of the treatment response

AML was diagnosed according to the WHO 2008 criteria and as described previously (25, 36). Cytogenetic studies were carried out using standard techniques. Molecular screening of fusion genes was offered to all patients. CR was defined as 5% bone...
marrow blasts, absence of blasts with Auer rods, absence of extramedullary disease, 1.0 $\times$ 10^9/L ANC, and 100 $\times$ 10^9/L PLT count. Early CR was defined as CR through one course of induction, while later CR referred to CR after more than one course of induction. Minimal residual disease (MRD) was defined as reported previously (37–40): $>$0.01% flow cytometry MRD-positive (FCM MRD+) cells from a leukemia-associated immunophenotype (LAIP) cell population in >1 bone marrow samples (a minimum of 7.5 $\times$ 10^6 events were collected); molecular MRD-positive (MOL MRD+), WT1 transcript level (calculated as percentage of target transcript copies/ABL copies) $>$0.6% in patients with MLL-AF9 (MLLT3-KMT2A)-negative, and the presence of MLL-AF9 transcript in MLL-AF9–positive patients (38). The simultaneous presence of FCM and MOL MRD+ statuses in one sample was defined as MRDCo+. 

Treatment protocols

Treatment involved 1–2 cycles of induction with IA-10 (idarubicin 10 mg/m² for 3 days in combination with cytarabine 100 mg/m² for 7 days) or HAA (homoharringtonine 2 mg/m² for 7 days, aclamycin 20 mg/day for 7 days, and cytarabine 100 mg/m² for 7 days). If CR occurred, patients received consolidation. Patients in the chemotherapy group received six cycles of consolidation, including four cycles of intermediate-dose cytarabine (2 g/m² every 12 hours for 3 days) and two cycles of anthracycline (daunorubicin 45 mg/m² or idarubicin 10 mg/m² for 3 days or mitoxantrone 8 mg/m² for 3 days) plus cytarabine (100 mg/m² for 7 days). When a suitable donor was available, eligible patients proceeded to undergo HSCT after receiving 2–4 cycles of consolidation therapy, including at least two cycles of intermediate-dose cytarabine plus 0–2 cycles of anthracycline plus cytarabine-based chemotherapy. All anthracyclines were calculated not to exceed the maximum cumulative lifetime dose (equivalent to 550 mg/m² for daunorubicin).

The protocol required DNA typing of the patient and donor for HLA-A, B, and DRB1 at high resolution. In haplo-HSCT, the patients received a graft from a family member with whom they shared one HLA haplotype but differed to a variable degree for HLA-A, -B, and DR antigens of the unshared HLA haplotype. G-CSF (5 mg/kg of body weight per day for 5 days) was used to mobilize the bone marrow and peripheral blood. The target mononuclear cell count was 6–8 $\times$ 10^9/kg of the recipient's weight. Bone marrow harvested on day 4 after G-CSF treatment and peripheral blood–stem cells harvested on day 5 after G-CSF treatment were infused into the recipient on the day of tissue collection. All haplo-HSCT patients received both bone marrow and peripheral blood mobilized with G-CSF.

The conditioning therapy for haplo-HSCT was as follows: intravenous cytarabine (4 g/m² per day) on days −10 to −9, intravenous busulfan (3.2 mg/kg per day) on days −8 to −6, intravenous cyclophosphamide (1.8 g/m² per day) on days −5 to −4, oral methyl chloride hexamethylene urea nitrate (Me-CCNU; 250 mg/m² per day) on day −3, and intravenous ATG (2.5 mg/kg per day; Sang Stat) on days −5 to −2. The GVHD prophylaxis regimen consisted of pretransplant ATG and posttransplant cyclosporine A, mycophenolate mofetil, and short-term methotrexate.

Between May 2012 and November 2013, 21 patients were randomized to receive low-dose corticosteroid prophylaxis (www.clinicaltrials.gov, NCT01607580).

Endpoints and statistical methods

LFS was the primary endpoint, which was defined as the survival period with continuous CR from CR1 after induction.
MRD was not considered relapse for LFS determination. Other endpoints included OS, CIR, and NRM in the whole study population, as well as GVHD-free, relapse-free survival (GRFS) in the haplo-HSCT cohort. Death from any cause was used as an event for OS, and survivors were censored at the date of last follow-up. Relapse was defined as a recurrence of >5% bone marrow blasts, reappearance of blasts in the blood, or the development of extramedullary disease infiltrates at any site. NRM was defined as death after HSCT or chemotherapy without disease progression or relapse. Acute GVHD (aGVHD) and chronic GVHD (cGVHD) was evaluated and graded by a single practitioner within the program (41). cGVHD was classified as limited or extensive and was also classified as mild, moderate, or severe by the NIH consensus criteria (42). GRFS events were defined as grade 3−4 aGVHD, systemic therapy−requiring cGVHD (extensive or NIH severe), relapse, or death in 3 years post-HSCT (43).

To exclude bias that may arise from including patients who relapsed or died too early to receive haplo-HSCT in CR1, landmark analysis (4 months after CR1) was used when comparing the outcomes of patients undergoing haplo-HSCT and those receiving chemotherapy. Comparisons of patient characteristics between the two groups were performed using the Mann–Whitney U test for continuous variables and the χ² test for categorical data. Under the null hypothesis H₀, the distributions of both populations are equal and P > 0.05. The survival functions were estimated by the Kaplan–Meier method using the log-rank test with asymmetric 95% confidence intervals (CI). The cumulative incidences of CIR was calculated using competing risks with aGVHD or cGVHD were calculated using competing risks with NRM and relapse. To adjust for differences in the baseline characteristics, left-truncated versions of the Cox proportional hazards regression models were used to evaluate the relative risk of subjects undergoing haplo-HSCT using chemotherapy as the reference in the models. The variables included in the univariate analysis were patient age (linear with estimates of HRs for 10-years’ difference), sex (female or male), white blood cell (WBC) count at diagnosis (linear with estimates of HRs for 10 × 10⁹/L difference), French-American-British (FAB) classification, cytogenetic (normal or other int-risk), molecular markers (MLL-AF9 or MLL-PTD vs. no specific marker), and courses before achieving CR1 (≤ 1 or >1 course). Age and WBC count at diagnosis were calculated as continuous variables. Variables included in the multivariate analysis were selected by backward elimination process with a criterion of P < 0.10 for retention. Two-way interactions were checked between each selected variable and main effect with χ² analysis; as well as bivariable analysis between variables to guarantee no significant interaction (Spearman correlation for non-normally distributed values; Pearson correlation for normally distributed values). To test whether a Cox proportional hazards model or time-dependent covariates Cox model should be constructed, all variables included in the multivariable analysis were tested for proportional hazards assumption.

A propensity score was calculated using multivariable logistic regression for each individual to minimize confounding when comparing the effectiveness of two postremission treatments. The propensity score included all factors tested in the univariate analysis except variables with interaction (Supplementary Table S2). The covariate balance was evaluated by the standardized absolute mean difference (SAMD), and adequate balance was considered at SAMD < 0.1. We calculated the adjusted HRs for LFS, OS, CIR, and NRM using standardized mortality ratio (SMR) weighting with corresponding propensity score in overall comparison and subgroup comparison (44–47). SPSS 22.0, R software 2.15, and GraphPad Prism 6.0 were used for data analyses and graphing.

**Results**

**Patient characteristics**

A total of 443 newly diagnosed patients with AML ages 15−60 years with int-risk cytogenetics were consecutively enrolled and underwent treatment at Peking University People’s Hospital (Beijing, China) between July 2010 and December 2014. The median follow-up was 48.6 months (36.1−88.5 months). Patients were excluded if they had FLT3+ (n = 79) or NPM1+–FLT3− mutations (n = 99) or experienced induction failure or death during induction (n = 27); the remaining patients (n = 238) achieved CR1. The median time to haplo-HSCT was 4 months (range 2−9 months) from achievement of CR1. Patients in CR1 were excluded from the landmark analysis (haplo-HSCT vs. chemotherapy) for the following conditions within 4 months after CR1: early relapse (n = 18), more than two courses of induction for CR1 (n = 19); underwent either MSD-HSCT (n = 39) or MUD-HSCT (n = 5); and withdrew from the trial with a high comorbidity score or ineligible for allo-HSCT (n = 10). The remaining patients (n = 147) were divided into the haplo-HSCT (n = 78) and chemotherapy (n = 69) groups. All 78 patients who underwent haplo-HSCT achieved sustained myeloid and PLT engraftment (Fig. 1).

**General characteristics of patients in CR1**

Of the 238 patients in CR1, 68 experienced relapse, which corresponds to a 3-year probability of CIR of 31.3% (95% CI, 22.5−40.5); this subgroup included 18 early relapses before reaching the landmark (within 4 months post CR1) and 37 relapses during consolidation after reaching the landmark (age > 40, n = 26; age ≤ 40, n = 11). Sixteen patients achieved a second CR (CR2; 30.9% of whom relapsed; age > 40, n = 14; age ≤ 40, n = 2), and 8 patients moved on to allo-HSCT. Thirteen cases of relapse occurred post-allo-HSCT (9 cases after haplo-HSCT, 2 after MSD-HSCT, and 2 after MUD-HSCT), and 4 patients achieved durable remission. In addition, 22 had NRM, including 15 who developed NRM post-allo-HSCT and 2 during consolidation. The 3-year probability of NRM was 11.9% (95% CI, 3.9−24.8), and the 3-year LFS and OS were 61.2% (95% CI, 54.2−67.4) and 68.3% (95% CI, 61.5−74.2), respectively (Fig. 2).

There were no significant differences in patient characteristics or transplantation outcomes between the 39 patients who underwent MSD-HSCT and the 5 patients who underwent MUD-HSCT, in line with previous reports (refs. 25, 48; Supplementary Fig. S1). As shown in Table 1, the groups were well matched, except that patients undergoing haplo-HSCT were significantly younger than those undergoing chemotherapy.

In the bivariable analysis, variables of MRD after first and second consolidation were interacted, CON-2 FCM MRD was selected by backward elimination process in multiple variable analysis for consideration of collinearity. All the P value of variables included in testing proportional hazard assumption were above 0.05, therefore the HR would be constant across time and the multivariate analysis was constructed in a Cox
proportional hazards model rather than the time-dependent covariates model.

**Comparative analysis of chemotherapy versus haplo-HSCT**

LFS. In univariate analysis, treatment option (haplo-HSCT vs. chemotherapy; HR 0.380; 95% CI, 0.218–0.663; P < 0.001) and Con-2 MRD status (FCM + vs. −; HR 1.861; 95% CI, 1.327–2.609; P < 0.001) were risk factors that affected LFS. Other variables, such as sex, WBC count at diagnosis, FAB classifications, normal versus abnormal cytogenetics, induction courses, and MRD status after the first consolidation, did not influence the risk of LFS (Supplementary Table S1). LFS was significantly lower in the chemotherapy group (3-year 47.3%, 95% CI, 33.4–59.9; 5-year estimated 42.0%, 95% CI, 26.6–56.7) than in the haplo-HSCT group (3-year 74.3%, 95% CI, 63.1–82.6; 5-year estimated 72.9%, 95% CI, 61.5–81.4; P = 0.0004; Fig. 3A).

The crude multivariate analysis suggested that treatment option (haplo-HSCT vs. chemotherapy; HR 0.356; 95% CI, 0.203–0.625; P < 0.001) and Con-2 FCM MRD (+ vs. −; HR 3.221; 95% CI, 1.773–5.911; P < 0.001) were independent risk factors affecting LFS (Table 2). To balance these factors across treatment groups, a propensity score was calculated for each patient. Age was identified as the only imbalanced factor between the haplo-HSCT and chemotherapy groups in the propensity score (Supplementary Table S2). Adequate balance after propensity score weighing was confirmed with SAMD < 0.1. Adjustment with the propensity score still suggested the same risk factors as those identified with the crude multivariate analysis (haplo-HSCT vs. chemotherapy; HR 0.360, 95% CI, 0.163–0.793, P = 0.011; Con-2 FCM MRD + vs. −; HR 3.903, 95% CI, 1.773–6.591, P = 0.001; Table 2). Then multivariate analysis were stratified by Con-2 FCM MRD status and two propensity score model were constructed in each subgroup (MRD + or −; Supplementary Table S2), the propensity score–adjusted multivariate analysis suggested that treatment option (haplo-HSCT vs. chemotherapy) were independent risk factors affecting LFS either in MRD + (HR 0.231; 95% CI, 0.078–0.684; P = 0.008) or MRD – subgroup (HR 0.420; 95% CI, 0.215–0.820; P = 0.011; Supplementary Table S3).

### OS

In the univariate analysis, treatment option (haplo-HSCT vs. chemotherapy; HR 0.321; 95% CI, 0.176–0.587; P < 0.001), Con-2 FCM MRD (+ vs. −; HR 1.514; 95% CI, 1.055–2.172; P = 0.024), and age (HR for 10-year difference, 1.308; 95% CI, 1.047–1.635; P = 0.018) affected OS; however, the other variables did not influence OS (Supplementary Table S1). OS was significantly lower in the chemotherapy group (3-year 53.5%, 95% CI, 39.6–65.6; 5-year estimated 37.6%, 95% CI, 34.9–40.5) than in the haplo-HSCT group (3-year 80.8%, 95% CI, 70.1–87.9; 5-year estimated 77.0%, 95% CI, 65.4–85.2; P = 0.001; Fig. 3B). The crude multivariate analysis suggested that treatment option (haplo-HSCT vs. chemotherapy; HR 0.316; 95% CI, 0.173–0.579; P < 0.001) and Con-2 FCM MRD (+ vs. −; HR 2.113; 95% CI,
1.115-4.007; \( P = 0.022 \)) were independent risk factors affecting OS. Propensity score adjustment confirmed haplo-HSCT as the only independent risk factor that improved OS (HR 0.361; 95% CI, 0.156-0.832; \( P = 0.017 \); Table 2). When stratified by Con2 FCM MRD, the propensity score-adjusted multivariate analysis confirmed haplo-HSCT as the only independent risk factor that improved OS either in MRD+ (HR 0.158; 95% CI, 0.041-0.614; \( P = 0.008 \)) or MRD− subgroup (HR 0.390; 95% CI, 0.196-0.775; \( P = 0.007 \); Supplementary Table S3).

Relapse. In the univariate analysis, treatment option (haplo-HSCT vs. chemotherapy; HR 0.170; 95% CI, 0.080-0.363; \( P < 0.001 \)), Con2 FCM MRD (+ vs. −; HR 2.214; 95% CI, 1.505-3.257; \( P < 0.001 \)), and age (HR for 1-year difference; HR 1.298; 95% CI, 1.013-1.664; \( P = 0.039 \)) were risk factors that affected CIR, whereas the other variables did not influence the risk of CIR (Supplementary Table S1). CIR was significantly higher in the chemotherapy group (3-year 49.0%; 95% CI, 34.5-62.2%) than in the haplo-HSCT group (3-year 11.7%; 95% CI, 1.4-34.4; \( P = 0.0001 \); Fig. 3C).

Table 1. Patient characteristics of the haplo-HSCT and chemotherapy groups

<table>
<thead>
<tr>
<th></th>
<th>Chemo (n = 69)</th>
<th>Haplo (n = 78)</th>
<th>( P )</th>
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<tbody>
<tr>
<td>Mean age, n (range), years</td>
<td>44 (21-60)</td>
<td>30 (16-58)</td>
<td>&lt;0.0001</td>
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<td>16-40 years, n (%)</td>
<td>27 (39.1)</td>
<td>60 (76.9)</td>
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<tr>
<td>41-60 years</td>
<td>42 (60.9)</td>
<td>18 (23.1)</td>
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<td>Sex, n (%)</td>
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<tr>
<td>Male</td>
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<tr>
<td>Female</td>
<td>32 (46.4)</td>
<td>39 (50)</td>
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<tr>
<td>Mean WBC, n (range) × 10^3/L</td>
<td>7.3 (0.7-210)</td>
<td>7.4 (0.6-155)</td>
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<td>&gt;40, n (%)</td>
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<td>18 (23.1)</td>
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<td>&lt;40</td>
<td>60 (87.0)</td>
<td>60 (76.9)</td>
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<td>Cytogenetic, n (%)</td>
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<td>Normal</td>
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<td>Abnormal</td>
<td>14 (20.3)</td>
<td>21 (26.9)</td>
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<tr>
<td>Courses to CR, n (%)</td>
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<td>1</td>
<td>47 (68.1)</td>
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<td>2</td>
<td>22 (31.9)</td>
<td>19 (24.4)</td>
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<td>Induction to CR, n (%)</td>
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<td>Courses before HSCT, n (%)</td>
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<td>MRD, n (%)</td>
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<td>Con-1 MRD−</td>
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<td>42 (60.9)</td>
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<td>NRM, n (%)</td>
<td>2 (2.9)</td>
<td>12 (15.4)</td>
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</table>

NOTE: Data are number of patients unless otherwise noted.

The crude multivariate analysis suggested that treatment option (haplo-HSCT vs. chemotherapy; HR 0.148; 95% CI, 0.069-0.317; \( P < 0.001 \)) and Con2 FCM MRD (+ vs. −; HR 0.338; 95% CI, 2.202-8.545; \( P < 0.001 \)) were independent risk factors for CIR. Propensity score adjustment did not alter the results observed from the crude multivariate analysis (haplo-HSCT vs. chemotherapy: HR 0.161; 95% CI, 0.057-0.459; \( P = 0.001 \); Con2 FCM MRD + vs. −; HR 0.454; 95% CI, 1.801-11.469; \( P = 0.001 \); Table 2). When stratified by Con2 FCM MRD, the propensity score-adjusted multivariate analysis suggested haplo-HSCT as the only independent risk factor that decreased CIR either in MRD+ (HR 0.161; 95% CI, 0.046-0.565; \( P = 0.004 \)) or MRD− subgroup (HR 0.138; 95% CI, 0.051-0.371; \( P = 0.001 \); Supplementary Table S3).

NRM. In the univariate and multivariate analyses, no variable correlated with the risk of NRM (Table 2). In competitive risk analysis, NRM was inferior in the haplo-HSCT group compared with that in the chemotherapy group (haplo-HSCT: 3-year 15.4%, 95% CI, 3.8%-34.9%; chemotherapy: 3-year 3.0%, 95% CI, 0-41.7; \( P = 0.02 \); Fig. 3D).
In the haplo-HSCT cohort, 7 patients (8.9%; 95% CI, 0.6–31.7) developed grade 3–4 aGVHD within 100 days post-HSCT and 8 patients (10.3%; 95% CI, 0.3–34.0) developed severe cGVHD requiring systemic therapy within 3 years. The 3-year GRFS of haplo-HSCT was 62.6% (95% CI, 50.8–72.3; Fig. 3E).

Subgroup analysis

For patients >40 years old, haplo-HSCT was superior to chemotherapy in terms of LFS (3-year 83.3% vs. 37.3%; \( P = 0.0018 \)), OS (3-year 88.9% vs. 44.7%; \( P = 0.0028 \)), and CIR (3-year 16.3% vs. 55.7%; \( P = 0.0008 \)). In patients \( \leq 40 \) years old, CIR was lower in the haplo-HSCT group than in the chemotherapy group (3-year 16.3% vs. 55.7%; \( P = 0.007 \)), while there was a trend but no statistical significance in terms of LFS (3-year 71.7% vs. 62.8%; \( P = 0.150 \)) and OS (3-year 78.3% vs. 64.1%; \( P = 0.0986 \)). Because the median age in the haplo-HSCT group was younger than that in the chemotherapy group, a propensity score–adjusted multivariate analysis was applied to balance these characteristics.

Age did not affect outcomes either in the haplo-HSCT or chemotherapy groups in terms of LFS (3-year 83.3% vs. 71.7%, \( P = 0.2974 \); 3-year 37.3% vs. 62.8%, \( P = 0.2726 \)), OS (3-year 88.9% vs. 78.3%, \( P = 0.5493 \); 3-year 55.7% vs. 31.4%,

Figure 3.
Outcomes of chemotherapy versus haplo-HSCT. LFS (A); OS (B); CIR (C); NRM (D); and GRFS (E).
Multivariate analyses of LFS, OS, CIR, and NRM (Table 2. n = 147)

Table 2. Multivariate analysis of LFS, OS, CIR, and NRM (n = 147)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LFS (HR, 95% CI)</th>
<th>OS (HR, 95% CI)</th>
<th>CIR (HR, 95% CI)</th>
<th>NRM (HR, 95% CI)</th>
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<tr>
<td>Haplo-HSCT Crude</td>
<td>0.356 (0.203–0.63)</td>
<td>0.366 (0.205–0.65)</td>
<td>0.148 (0.069–0.317)</td>
<td>0.148 (0.069–0.317)</td>
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<tr>
<td>Adjusted</td>
<td>0.316 (0.173–0.579)</td>
<td>0.316 (0.173–0.579)</td>
<td>0.161 (0.098–0.283)</td>
<td>0.161 (0.098–0.283)</td>
</tr>
<tr>
<td>Con2 FCM Crude</td>
<td>0.366 (0.205–0.65)</td>
<td>0.366 (0.205–0.65)</td>
<td>0.161 (0.098–0.283)</td>
<td>0.161 (0.098–0.283)</td>
</tr>
<tr>
<td>Adjusted</td>
<td>0.316 (0.173–0.579)</td>
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<td>0.161 (0.098–0.283)</td>
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Conclusions and Impact of Haplo-HSCT

In the chemotherapy group, Con2 FCM MRD+ had inferior survival compared with Con2 FCM MRD− in terms of LFS (3-year 17.8% vs. 59.1%; P = 0.0002), OS (3-year 21.3% vs. 62.0%; P = 0.0028), and CIR (3-year 80.4% vs. 39.6%; P = 0.004). Con2 FCM MRD status was not associated with outcomes in haplo-HSCT group in terms of OS (83.3% vs. 80.3%; P = 0.8059) and perhaps LFS (3-year 50.0% vs. 78.8%; P = 0.00714; Supplementary Fig. S3). MRD status was also not correlated with the risk of NRM (Supplementary Table S3).

Discussion

This study presents the first prospective assessment related to the controversial issue of whether patients with int-risk AML would benefit from haplo-HSCT compared with chemotherapy during CR1. Although the study was nonrandomized, it is strengthened by its prospective nature, its diagnosis-driven, unselected real-world cohort, uniform treatment modality, and improved statistical methods with propensity score adjustments to simulate the randomized situation.

Currently, haplo-HSCT is recommended as a valid postremission therapy for patients with high-risk AML in the absence of MSDs or MUDs and who require an urgent transplant procedure (18). However, for int-risk AML, although it is advocated that some patients could achieve CR2 and that the outcomes of CR1 and CR2 are similar post-allo-HSCT, the CR2 rates in relapsing int-risk patients are lower (35%), and patients actually proceeding to allo-HSCT during CR2 are compromised (9). Cornelissen and colleagues conducted an MSD versus no donor analysis and reported that patients with int-risk AML had better survival, while allo-HSCT with either MSDs or MUDs was superior to chemotherapy (5-year LFS 56% vs. 28%; HR 0.47; 95% CI, 0.35–0.63; P < 0.001) in patients with int-risk AML (11, 49). Therefore, allo-HSCT with MSDs or MUDs was generally recommended for patients with int-risk AML in CR1. In contrast, limited data are available regarding the role of haplo-HSCT in patients with int-risk AML, as most reports involved a heterogeneous population of patients with AML including those who achieved CR or presented active disease (22–24, 50, 51), and the recommendations were uncertain (18, 31). The development of haplo-HSCT with comparable outcomes with MSDs and MUDs urged us to readdress this controversial question.

Compared with a previous study of haplo-HSCT versus chemotherapy in patients with int- or high-risk AML (32), this study incorporated several improvements. (i) This work established the cytogenetic plus molecular int-risk group according to NCCN 2009 criteria instead of heterogeneous populations of cytogenetic int- and high-risk patients (considering that patients with high-risk might benefit more from haplo-HSCT). (ii) Landmark analysis of patients was conducted at 4 months post CR1. Patients with a
high-comorbidity score or low-performance score were withdrawn from the cohort, and patients with early relapse were excluded from the comparison rather than included in the chemotherapy group, thus possibly avoiding bias arising from including patients who are not eligible to receive allo-HSCT in the chemotherapy group. The most common causes for patients not receiving transplantation during CR1 are relapse within 6 months and poor performance status (12). (iii) The protocol implemented improved statistical methods using a propensity score–adjusted Cox model with imbalanced factors (especially age), which may help eliminate the bias arising from imbalanced patient characteristics between the haplo-HSCT and chemotherapy groups (44–46). (iv) Finally, prospective data from consecutive patients who received all in-hospital treatments at a single institution from their initial diagnosis were included, which may avoid the bias of selecting younger patients with a good performance score from different institutes around the nation. Furthermore, no patients overlapped with the previous study, which enrolled patients from Jan 2006 to May 2010 (32). These advantages may help further resolve the controversial issue of haplo-HSCT versus chemotherapy in individuals with this disease.

In this study, we found that compared with chemotherapy alone, haplo-HSCT confers survival advantages in terms of LFS, OS, and CIR. The outcomes of the chemotherapy group in this study (3-year LFS 47.3%, OS 53.5%, CIR 48.1%, and NRM 3.0%) were comparable with those of the high-dose cytarabine (HDAC) subgroup of the Southwest Oncology Group (SWOG) trial (4-year LFS 33%; OS 32%; ref. 52), patients with int-risk AML in the HOVON/SAKK trial (4-year OS 48%; LFS 41%; ref. 49), and Cornilens and colleagues’ latest report in patients ages 40–60 (5-year OS 36%, LFS 28%, CIR 70%, and NRM2%; ref. 11). Although homoharringtonine-based induction therapy is less common in Europe and North America, this induction protocol is comparable with the daunorubicin-based protocol (53), and the rates of early and late CR in this study were similar to those in the HOVON/SAKK trial (72% vs. 81% and 28% vs. 19%). In addition, LFS and OS following haplo-HSCT in this study are comparable with those described in a previous report of haplo-HSCT with ATG+G-CSF protocol (13%–25% vs. 41%–45%; ref. 54). Thus, the basis of this study is valid to address the proposed question.

The superiority of haplo-HSCT over chemotherapy can mainly be attributed to two aspects: whether haplo-HSCT exerts a strong graft-versus-leukemia (GVL) effect to reduce CIR and its ability to maintain a relatively low NRM (4). First, in addition to the comparison of CIR between two groups, inclusion of an MRD assessment before and after HSCT can help evaluate whether HSCT can overcome the negative effect of MRD status on relapse. In this study, MRD status after consolidation as evaluated by FCM was identified as an independent risk factor for increasing CIR and decreasing LFS/OS in the chemotherapy group but was not significant in the haplo-HSCT group. This result is in accordance with our previous report that haplo-HSCT is superior to MSD-HSCT in eradicating pretransplantation FCM MRD in patients with AML (55). Nevertheless, although there was a trend toward increased CIR for patients with Con-2 FCM MRD+ compared with patients with MRD−, the improved OS might be due to multiple donor lymphocyte infusions preventing a second relapse (56).

In addition, considering that the significance of pretransplant MRD was not well established in this study and our previous report (57), it would be appropriate to reconsider the transplantation decisions after the second consolidation, consistent with integrated risk profiles recommended by Cornelissen and colleagues (6, 58). However, caution must be taken in interpreting these results due to the relatively small subgroup of different MRD statuses. Second, NRM has continuously improved with haplo-HSCT with either the PT-CY (7%–22%; refs. 59, 60) or ATG+G-CSF protocol (13%–18%; refs. 61, 62) compared with early T-cell–depleted haplo-HSCT procedures (30%–54%; refs. 21, 26, 33). Especially among patients ages 40–60 years, the rate of NRM did not increase with age following myeloablative conditioning, which is in accordance with our previous report that the outcomes of older patients (age >50 years) were comparable with those of younger patients (63). Therefore, currently, NRM is no longer a limiting factor in increasing survival benefits from haplo-HSCT. On the basis of available evidence-based studies, the consensus from the Chinese Society of Hematology from 2018 stated that patients with int-risk AML were recommended to undergo allo-HSCT irrespective of donor source (64).

The major limitation of our current study is that patients were not randomized to undergo haplo-HSCT with ATG+G-CSF or receive chemotherapy alone for ethical and practical reasons. Although propensity score adjustment and landmark analysis were introduced to minimize the imbalanced features to some extent, the significance of these methods cannot not be overemphasized. In addition, patients with int-risk AML who achieved CR1 (3–5 year LFS 63%–74%; OS 68%–79%; refs. 44, 46, 65) and results of propensity score adjustment should be interpreted with caution for potential bias (66). Second, this trial was designed 9 years ago according to risk criteria from NCCN 2009, and the definition of int-risk AML has continued to evolve based on emerging biomarkers, such as the FLT3-ITD allelic ratio, biallelic mutated CEBPA, mutated TP53, mutated RUNX1, and mutated ASXL1, all of which are in the present ELN or NCCN recommendations (4, 5). Specifically, considering that CEBPA is enriched in younger patients and that RUNX1/ASXL1/TP53 mutations are enriched in elderly patients, there may be potential biases linked to the presence of these alterations due to the unbalanced age distribution in the two study arms. In addition, patients with int-risk AML with mutated NPM1 with FLT3-ITDhigh or wild-type NPM1 with FLT3-ITDlow were not included in this trial due to the absence of the FLT3-ITD allelic ratio data. Therefore, the results of this trial should be interpreted with caution because of the new int-risk definition. Future trials may consider adding these biomarkers to further reduce heterogeneity. Third, some of the study designs were not in strict accordance with the NCCN or ELN guidelines, which might increase the difficulty of extrapolating these findings to those of other nations. For example, the use of homoharringtonine and aclamycin in the induction protocols, the addition of two cycles of an anthracycline combined with cytarabine to the four cycles of cytarabine administered as a single agent in consolidation, and the 2–4 cycles of consolidation before HSCT do not adhere to the above mentioned guidelines. Nevertheless, as the rates of early and late CR, as well as of LFS OS in this study were comparable with other reports that strictly followed the NCCN/ELN recommended protocol and the characteristics of patients were comparable between the two groups at the landmark point.
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(early/late CR, MRD, EOCOG, HCT-CI, etc.), this study still has merit in the primary goal of comparing haplo-HSCT with chemotherapy in the postremission treatment of int-risk AML CR1. Finally, due to the relatively small sizes of the subgroups, the survival analysis of the subgroups should be interpreted with caution.

In summary, this study suggests that myeloablative haplo-HSCT with ATG+G-CSF might be superior to chemotherapy as a postremission treatment for patients with AML with int-risk during CR1. Haplo-HSCT is a feasible postremission therapy for int-risk AML in the absence of MSDs and MUDs.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors’ Contributions

Conception and design: X.-J. Huang
Development of methodology: Y. Wang, Y.-J. Chang, X.-J. Huang
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M. Lv, Y. Wang, Y.-J. Chang, X.-H. Zhang, Q. Jiang, H. Jiang, J. Liu, H. Chen, W. Han, F.-R. Wang, J.-Z. Wang, Y. Chen, Y.-Y. Zhang, Y.-Q. Sun, H.-H. Zhu, J.-S. Jia, T. Zhao, J. Wang, K.-Y. Liu, X.-J. Huang
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M. Lv, Y. Wang, Y.-J. Chang, Q. Jiang, H.-H. Zhu, X.-J. Huang

References


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Myeloablative Haploidentical Transplantation Is Superior to Chemotherapy for Patients with Intermediate-risk Acute Myelogenous Leukemia in First Complete Remission

Meng Lv, Yu Wang, Ying-Jun Chang, et al.


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