


LETTER TO THE EDITOR

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# Comparison of haplo-SCT and chemotherapy for young adults with standard-risk Ph-negative acute lymphoblastic leukemia in CR1

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## Abstract

Human leukocyte antigen (HLA) haploidentical stem cell transplantation (haplo-SCT) as a postremission treatment for standard risk Philadelphia chromosome-negative acute lymphoblastic leukemia (SR Ph-ALL) in the first complete remission (CR1) has not been defined. In this multicenter, phase 3 study (NCT02042690), of the 131 consecutive Ph-ALL young adult patients (YA, aged 18–39 years) without high-risk features who achieved CR1, 114 patients without HLA-matched donors received consolidation with an adult chemotherapy regimen ( $n = 55$ ) or haplo-SCT ( $n = 59$ ). In the landmark analysis, haplo-SCT resulted in a lower 2-year cumulative incidence of relapse (CIR, 12.8% vs 46.7%,  $P = 0.0017$ ) and superior 2-year leukemia-free survival (LFS, 80.9% vs 51.1%,  $P = 0.0116$ ) and 2-year overall survival (OS, 91.2% vs 75.7 [64.8–93.2] %,  $P = 0.0408$ ) than chemotherapy. In the time-dependent multivariate analysis with propensity score adjustment, postremission treatment (haplo-SCT vs chemotherapy) was an independent risk factor for the CIR (HR 0.195, 95% CI 0.076–0.499,  $P = 0.001$ ), LFS (HR 0.297, 95% CI 0.131–0.675,  $P = 0.003$ ), and OS (HR 0.346, 95% CI 0.140–0.853,  $P = 0.011$ ). In all subgroups, CIR was lower in haplo-SCT. Myeloablative haplo-SCT with ATG+G-CSF might be one of the preferred therapies for YA patients with standard-risk Ph-ALL.

**Trial registration:** [ClinicalTrials.gov](https://clinicaltrials.gov). Registered on 23 January 2014, <https://clinicaltrials.gov/ct2/show/NCT02042690>

**Keywords:** Haplo-SCT, Adult chemotherapy, Ph-negative acute lymphoblastic leukemia

## To the Editor:

Philadelphia chromosome-negative acute lymphoblastic leukemia (Ph-ALL) is categorized as high risk (HR) with risk factors such as advanced age, elevated WBC count, and high-risk cytogenetic abnormalities.

The remaining older adolescents and young adults (AYA, aged 15–39 years) without risk factors are AYA with standard-risk (SR) Ph-ALL and represent a group with lower cumulative incidence of relapse and better overall survival. Allogeneic hematopoietic stem cell transplantation (allo-SCT), especially from human leukocyte antigen (HLA)-matched sibling donors (MSDs) or matched unrelated donors (MUDs), is one of the preferred options over chemotherapy in the consolidation treatment of Ph-ALL [1, 2]. However, the shortage of MSDs and limited availability of MUDs prevents large populations from benefiting from allo-SCT [3].

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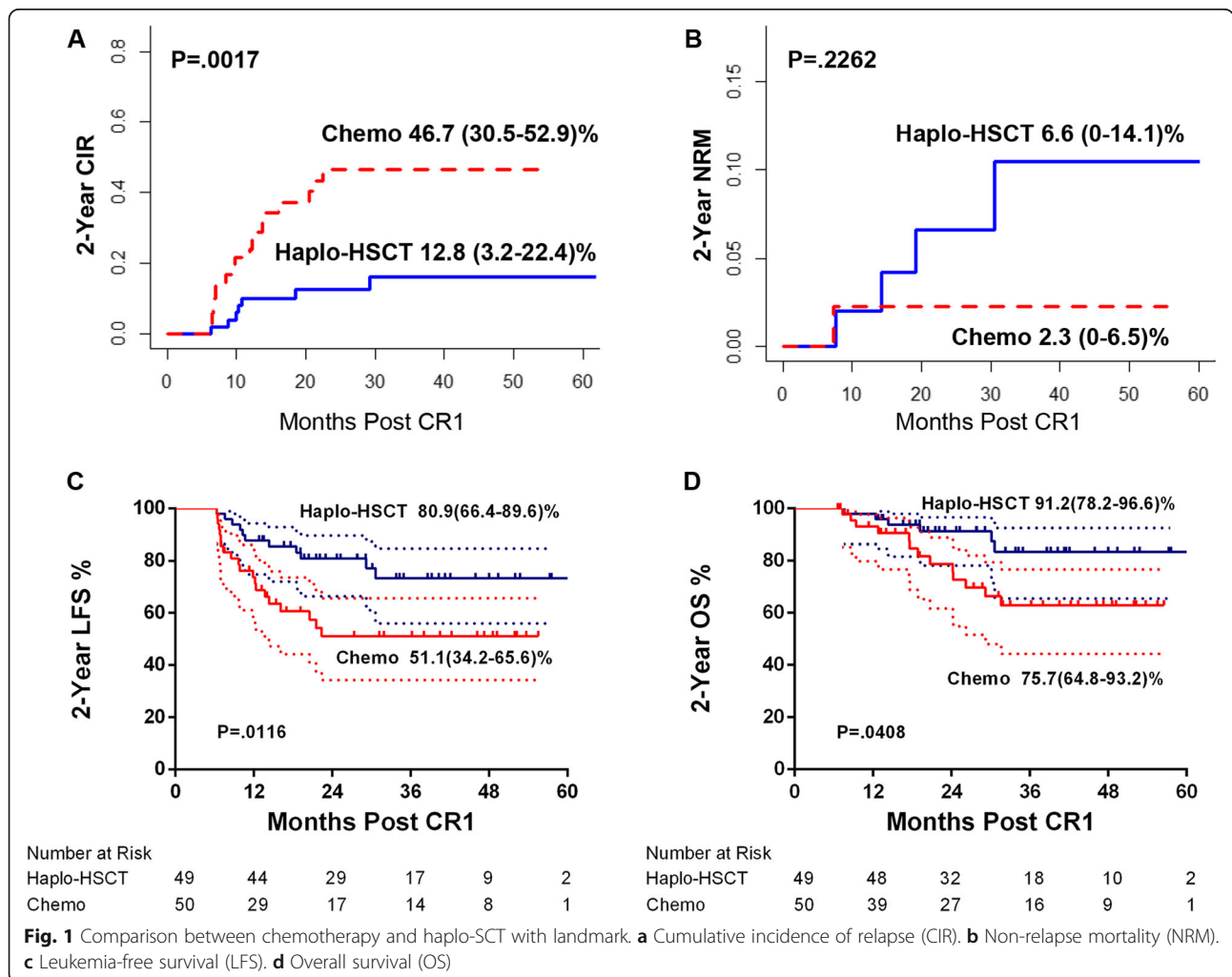
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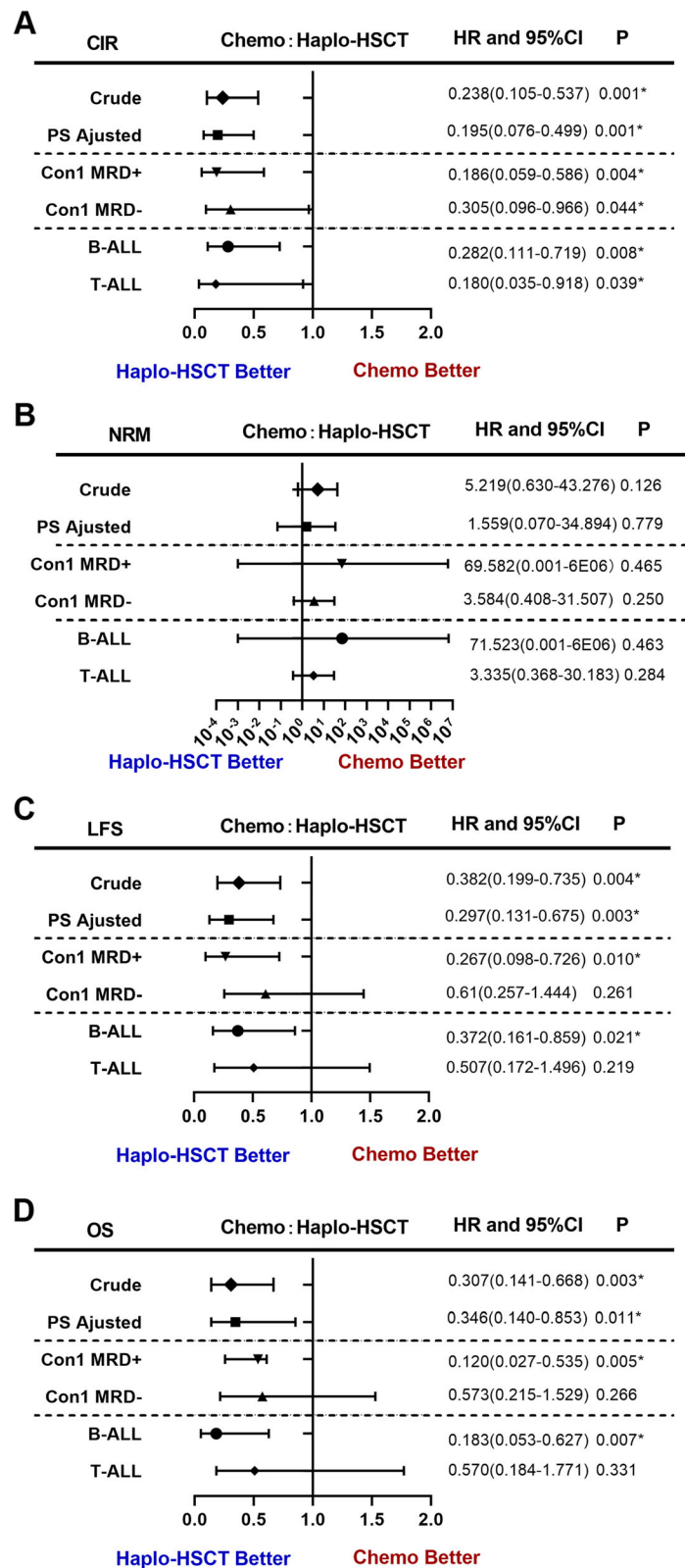
Recently, unmanipulated haploidentical SCT (haplo-SCT) using pretransplant ATG and granulocyte colony-stimulating factor (G-CSF)-stimulated grafts (ATG+G-CSF) or posttransplant cyclophosphamide (PT-CY) protocol was confirmed equivalent to HLA-matched SCT in ALL [4–6]. However, as prospective data is absent, it is unknown whether AYA SR Ph-ALL patients should pursue haplo-SCT instead of consolidation chemotherapy in the absence of MSDs and MUDs [7, 8]. This multicenter prospective clinical trial was registered at <https://clinicaltrials.gov> as NCT02042690 (Suppl Method).

In total, 131 consecutive Ph-ALL young adult patients (YA, aged 18–39 years) without high-risk features who achieved CR1 were enrolled with a median follow-up of 32 months (Figure S1, Table S1). haplo-SCT was superior to chemotherapy in terms of lower CIR and improved LFS and OS in total enrolled CR1 patients without landmark (Figure S2); haplo-SCT was also associated with lower CIR and improved LFS in the subgroup of patients who took only 1 cycle to achieve CR and been MRD negative after Con-1 (Figure S3).

Dynamic landmark suggested haplo-SCT was associated with lower CIR and improved LFS and OS compared with chemotherapy between 0 and 12 months post-CR1 (Figure S4). Then, 6 months was chosen as the fixed landmark point, relapse or NRM before 6 months post-CR1 ( $n = 15$ ) was excluded, those undergoing SCT after the landmark were included in the chemotherapy group, and the remaining patients ( $n = 99$ ) were divided into the haplo-SCT group ( $n = 49$ ) and chemotherapy group ( $n = 50$ ) (Table S2). In landmark analysis, CIR (2-year CIR 12.8%, 95% CI 3.2–22.4 vs 46.7%, 95% CI 30.5–52.9%;  $P = 0.0017$ ), LFS (2-year LFS 80.9%, 95% CI 66.4–89.6 vs 51.1%, 95% CI 34.2–65.6%;  $P = 0.0116$ ), and OS (2-year OS 91.2%, 95% CI 78.2–96.6% vs 75.7%, 95% CI 64.8–93.2%;  $P = 0.0408$ ) continued to be better in the haplo-SCT group than in the chemotherapy group (Fig. 1a, c, d), while NRM was comparable (Fig. 1b).

Cox PH regression model was constructed considering the time of haplo-SCT as a time-dependent exposure based on PH test (Table S3). Univariate analysis for CIR,





**Fig. 2** Forest plot of time-dependent multivariable Cox regression model. **a** Cumulative incidence of relapse (CIR). **b** Non-relapse mortality (NRM). **c** Leukemia-free survival (LFS). **d** Overall survival (OS)

NRM, LFS, and OS was listed in Table S4. Both crude- and PS-adjusted multivariate analyses suggested haplo-SCT was associated with lower CIR (PS-adjusted HR 0.195, 95% CI 0.076–0.499,  $P = 0.001$ ) and improved LFS (PS-adjusted HR 0.297, 95% CI 0.131–0.675,  $P = 0.003$ ) and OS (HR 0.346, 95% CI 0.140–0.853,  $P = 0.011$ ) compared with chemotherapy. Con1 FCM MRD (+ vs –) was an independent risk factor for CIR (PS-adjusted HR 3.609, 95% CI 1.562–8.340,  $P = 0.006$ ) and LFS (PS-adjusted HR 2.825, 95% CI 1.298–6.152,  $P = 0.009$ ). Diagnosis (T vs B; HR 2.564, 95% CI 1.361–4.823,  $P = 0.014$ ) was an independent risk factor for OS. No independent risk factors identified for NRM. When stratified by Con-1 MRD and diagnosis, haplo-SCT decreased CIR in all subgroups (Con-1 MRD+ vs MRD–, B-ALL vs T-ALL) while improved LFS and OS only in the Con-1 MRD+ and B-ALL subgroups but not in the Con-1 MRD– and T-ALL subgroups (Table S5, Fig. 2).

Currently, haplo-SCT is only an optional rather than a preferred choice for postremission therapy compared with MSD or 10/10 MUD-SCT. MSD-SCT is the preferred treatment for ALL, and MUD is also acceptable in most countries [7]. This study presents the first prospective assessment related to the controversial issue whether YA patients with SR ALL benefit more from haplo-SCT than adult chemotherapy regimen. The advantages of a low CIR and an acceptable NRM resulted in promising results of haplo-SCT in the present study, which were comparable to those in previous reports (5-year LFS 68.7%, OS 70.1%) [5, 8]. As NRM of haplo-SCT has generally improved with either the PT-CY (7 to 23%) or ATG+G-CSF protocol (11–13%) compared with early procedures [4, 9, 10], NRM might no longer be a limiting factor of receiving haplo-SCT, especially in experienced centers. Haplo-SCT was associated with lower CIR in both the Con-1 MRD +/- subgroups in the current study; meanwhile, cautions must be taken as CIR of non-SCT cohort might be higher compared with previous reports (46–49%) [1, 2]. More recently, some studies suggested pediatric-inspired regimens might further decrease the CIR to 12–33% and result encouraging survival (3–5 years LFS 59–73%, OS 60–79%) compared with adult regimen [11], while some reported similar outcomes [12]. Currently, guidelines tried to recommend the regimens both by adult and pediatric settings as adult regimens were still widely used, especially in developing countries [13, 14]. In addition, blinatumomab, which might further decrease CIR in MRD+ALL [15], was not available in the current study. Therefore, it remained to be addressed the role of haplo-SCT in the era of pediatric-inspired regimens and blinatumomab in the future.

The present study might be one of the best available evidence to compare haplo-SCT and adult

chemotherapy for YA SR Ph-ALL in CR1. Cautions must be taken in interpreting these results due to non-randomized design and a relatively small group of patients. Haplo-SCT might become one of the preferred therapies for YA patients with SR Ph-ALL in the absence of MSD or MUD-SCT.

### Supplementary information

Supplementary information accompanies this paper at <https://doi.org/10.1186/s13045-020-00879-1>.

**Additional file 1:** Supplementary figures.

**Additional file 2:** Supplementary tables.

**Additional file 3:** Supplementary methods.

### Abbreviations

allo-SCT: Allogeneic hematopoietic stem cell transplantation; AYA: Adolescents and young adults; CIR: Cumulative incidence of relapse; G-CSF: Granulocyte colony-stimulating factor; GRFS: GVHD-free, relapse-free survival rates; GVHD: Graft-versus-host disease; haplo-SCT: Haploidentical SCT; HLA: Human leukocyte antigen; HR: High risk; LFS: Leukemia-free survival; MRD: Minimal residual disease; MSDs: Matched sibling donors; MUDs: Matched unrelated donors; NRM: Non-relapse mortality; OS: Overall survival; Ph-ALL: Philadelphia chromosome-negative acute lymphoblastic leukemia; PS: Propensity score; PT-CY: Posttransplant cyclophosphamide; SR: Standard-risk

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### Authors' contributions

X-JH designed the study. ML, QJ, D-BZ, YH, D-HL, D-PW, and J-B.W collected the data. ML, QJ, Y-JC, and X-JH analyzed the data and drafted the manuscript. All authors contributed to the data interpretation and manuscript preparation and approved of the final version of the manuscript.

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### Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

### Ethics approval and consent to participate

This study was approved by the ethical review committees of all participating centers.

### Consent for publication

Written informed consent was obtained from all patients.

### Competing interests

The authors declare that they have no competing interests.

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