Allogeneic Hematopoietic Stem Cell Transplantation, Especially Haploidentical, May Improve Long-Term Survival for Children with High-Risk T-Cell Acute Lymphoblastic Leukemia in First Complete Remission

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**Abstract**

**Background:** The role of allogeneic hematopoietic stem cell transplantation (allo-HSCT) for children with high-risk (HR) T-cell acute lymphoblastic leukemia (T-ALL) in first complete remission (CR1) is still under critical discussion. Moreover, relapse is still the main factor affecting survival. This study explored the effect of allo-HSCT (especially haploidentical HSCT (haplo-HSCT) ) on improving survival and reducing relapse for children with HR T-ALL in CR1 and the prognostic factors of childhood T-ALL in order to identify who could benefit from HSCT.

**Methods:** Seventy-four newly diagnosed pediatric T-ALL patients were included in this study and stratified into low-risk chemotherapy cohort (n=16), high-risk chemotherapy cohort (n=31) and high-risk transplant cohort (n=27). The characteristics, survival outcomes and prognostic factors of all patients were analyzed.

**Results:** Patient prognosis in the high-risk chemotherapy cohort was significantly inferior to the low-risk chemotherapy cohort (5-year overall survival (OS): 51.2%±10% vs. 100%, \( P = 0.003 \); 5-year event-free survival (EFS): 48.4%±9.8% vs. 93.8%±6.1%, \( P = 0.01 \); 5-year cumulative incidence of relapse (CIR): 45.5%±0.8% vs. 6.3%±0.4%, \( P = 0.043 \)). For high-risk patients, allo-HSCT could improve the 5-year EFS and CIR compared to chemotherapy (5-year EFS: 77.0%±8.3% vs. 48.4%±9.8%, \( P = 0.041 \); 5-year CIR: 11.9%±0.4% vs. 45.5%±0.8%, \( P = 0.011 \)). 5-year OS in high-risk transplant cohort had a trend for better than that in high-risk chemotherapy cohort ( 77.0%±8.3% vs. 51.2%±10%, \( P = 0.084 \) ). Haplo-HSCT could reduce relapse and had a trend for improving long-term survival for HR patients when compared to the high-risk chemotherapy cohort (5-year OS: 80.0%±8.9% vs. 51.2%±10%, \( P = 0.093 \); 5-year EFS: 80.0%±8.9% vs. 48.4%±9.8%, \( P = 0.047 \); 5-year CIR: 13.9%±0.6% vs. 45.5%±0.8%, \( P = 0.022 \)). Minimal residual disease (MRD) re-emergence was the independent risk factor associated with 5-year OS, EFS and CIR.

**Conclusions:** allo-HSCT, especially haplo-HSCT, might effectively improve the survival outcomes for HR childhood T-ALL in CR1.

**Background**

T-cell acute lymphoblastic leukemia (T-ALL), an aggressive malignancy associated with poor prognosis, accounts for 10–15% of all pediatric ALL cases[1–4]. With the advent of various intensive combination chemotherapy regimens in recent years, the 5-year overall survival (OS) and event-free survival (EFS) rates have significantly increased to 71.9%-91.4% and 64%-87.8%, respectively for children with T-ALL[2, 3, 5–8]. However, patients with high-risk (HR) childhood T-ALL have shown unsatisfactory long-term OS and EFS of less than 50%[9–12]. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is sometimes recommended for children at first complete remission (CR1) showing HR characteristics and often recommended for patients at second or later CR[13]. But children with T-ALL at CR2 or later CR had significantly worse prognosis even if they were treated with allo-HSCT. In the past study in our institution, the 3-year leukemia-free survival (LFS) for children with T-ALL at CR2 or later CR was only 26.0% and 3-
year CIR was 56.7\%[14]. Few studies have demonstrated that the dismal prognosis of HR childhood T-ALL could be improved with allo-HSCT[9, 15, 16]. In the German ALL- Berlin-Frankfurt-Munster (BFM) 90 and 95 studies, the 5-year OS and 5-year disease-free survival (DFS) of patients who received allo-HSCT in CR1 was 67\%, and patients who treated with chemotherapy alone were 47\% and 42\% respectively[9]. Therefore, a risk-stratified approach to treat childhood T-ALL is warranted. In recent years, haploidentical HSCT (haplo-HSCT) has become an importantly alternative choice for many T-ALL children undergoing transplantation who could not find a matched related or unrelated donor. Moreover, it has proven to be a safe and effective option at our institution previously[14, 17–20]. To our knowledge, there have been fewer reports on the effects of chemotherapy compared to allo-HSCT, especially haplo-HSCT for HR childhood T-ALL, and the hierarchical criteria for HR groups remain unclear. Thus, this study aimed to explore the hierarchical criteria, prognostic factors of childhood T-ALL, and the role of allo-HSCT, especially haplo-HSCT, for children with HR T-ALL in CR1.

Methods

Patients

The clinical characteristics and outcomes of 77 pediatric patients (aged 1–18 years) with newly diagnosed T-ALL between 1 January 2012 and 30 June 2018 were collected. Patients were divided into different groups as described in Fig. 1. Seventy-four patients received induction chemotherapy while three patients died at the initial stage of treatment. Patients were assigned to two different chemotherapy regimens: the modified ALL- BFM protocol[21] or the Chinese Children Leukemia Group (CCLG)-ALL 2008 protocol[22]. We recommend that patients in the low-risk group choose chemotherapy, and patients in the high-risk group choose bone marrow transplantation. All decisions were based on patient preferences.

Definition of high-risk group

The high-risk group was defined by the presence of at least one of the following criteria: (1) failure to achieve CR after induction chemotherapy (d33)[23,24]; (2) MRD level $\geq 1 \times 10^{-4}$ in bone marrow aspirate three months after initial diagnosis[1,11,25,26]; (3) age $\geq 10$ years[2,23] and (4) re-emergent MRD.

Definitions and evaluations

Complete remission was defined as bone marrow (BM) leukemic blasts <5\% with regenerating hematopoiesis (platelet count $>100 \times 10^9$/l, neutrophils $>1 \times 10^9$/l) and no localised leukemic infiltrates. MRD of bone marrow was tested by flow cytometry (FCM) and/or quantitative PCR[27-29]. MRD positivity was defined as FCM$\geq 1 \times 10^{-4}$, including positive detection of other mutated genes ($SIL/TAL1, t(v; 11q23)/MLL$-rearranged). Relapse was defined as recurrence of $\geq 5$% BM leukemic blasts and/or localized leukemic infiltrates at any site.

OS was defined as time from diagnosis to death from any cause or the the date of final follow-up. EFS was defined as time from diagnosis to relapse, second tumor, death or the date of final follow-up. CIR
was calculated from CR1 to first relapse.

**Transplantation**

After induction therapy and at least 2 rounds of consolidation therapy, patients who achieved CR1 underwent a myeloablative transplant without total body irradiation (TBI) in accordance with their guardians’ wishes. The preconditioning regimen for MSD transplants was a modified busulfan-cyclophosphamide (Bu-Cy) conditioning regimen that included hydroxyurea (80 mg/kg/day, p.o., on day -10); cytarabine (2 g/m\(^2\)/day, i.v., on day -9); Bu (3.2 mg/kg/day, i.v., on days -8 to -6); Cy (1.8 g/m\(^2\)/day, i.v., on days -5 to -4); and methyl-N-(2-chloroethyl)-N-cyclohexyl-N-nitrosourea (Me-CCNU, 250 mg/kg/day, p.o., on day -3). The preconditioning regimen for haplo-transplants consisted of cytarabine (4 g/m\(^2\)/day, i.v., on days -10 to -9); Bu, Cy, Me-CCNU were same as above; and anti-thymocyte immunoglobulin (ATG, 2.5 mg/kg/day, i.v., on days -5 to -2). Granulocyte colony-stimulating factor (G-CSF) was provided to all transplant recipients to mobilize BM cells plus peripheral blood stem cells (PBSC). Short-term methotrexate (MTX), mycophenolate mofetil (MMF) and cyclosporine A (CsA) were provided to all transplant recipients for preventing graft versus host disease (GVHD). Supportive care was previously detailed[14,17-20].

**Statistics**

The variance analysis, Mann–Whitney U test, Kruskal–Wallis H test, chi-square test or Fisher’s exact test were used for comparison of clinical characteristics of different groups. The Kaplan-Meier method and Log-rank test were used for survival analysis. CIR was calculated by competing risk analysis. Factors with \( P < 0.1 \) in univariate analysis were adjusted in multivariate analysis by Cox regression model and \( R \leq 0.05 \) indicated statistical significance. All statistical analyses were primarily conducted using R software packages (Bell Labs, New Providence, NJ) and SPSS 26.0 (SPSS Inc., Chicago, IL, USA).

**Results**

**Patient characteristics**

From 1 January 2012 to 30 June 2018, 77 pediatric patients were newly diagnosed with T-ALL. One patient died prior to induction chemotherapy while two other patients died at the initial stage of induction chemotherapy due to pulmonary hemorrhage and heart damage respectively. The median age of remaining 74 patients admitted to this study was 11 years (range, 2–15). The last follow-up was 1 May 2020 and median follow-up time was 51.2 months (range, 22.1–99.3). The clinical characteristics of patients are summarized in Table 1.

**Table 1** Characteristics of all 74 T-ALL patients
| Parameter                          | All Patients Cohort (N=74) | Low-risk Chemotherapy Cohort (n=16) | High-risk Chemotherapy Cohort (n=31) | High-risk Transplant Cohort (n=27) | P     |
|-----------------------------------|---------------------------|------------------------------------|-------------------------------------|-----------------------------------|-------|
| Age, yr                           |                           | 0.261                              |                                     |                                   |       |
| Median (range)                    | 11(2-15)                  | -                                  | 11(3-15)                            | 12(4-15)                          |       |
| Sex, male/female                  | 52/22                     | 10/6                               | 21/10                               | 21/6                              | 0.520 |
| WBC count, ×10⁹/L                 |                           |                                    |                                     |                                   | 0.857 |
| Median (range)                    | 73.7(1.1-691.9)           | 72.5(1.8-691.9)                    | 87.6(1.1-614.8)                     | 60.5(1.4-629.3)                   |       |
| Hemoglobin, g/L                   |                           |                                    |                                     |                                   | 0.308 |
| Median (range)                    | 108(40-157)               | 97(59-124)                         | 104(50-146)                         | 114(40-157)                       |       |
| Platelet count, ×10⁹/L            |                           |                                    |                                     |                                   | 0.463 |
| Median (range)                    | 57(8-461)                 | 51(10-399)                         | 75(12-461)                          | 57(8-390)                         |       |
| ETP/Non-ETP                       | 13/58                     | 2/14                               | 4/26                                | 7/18                              | 0.361 |
| SIL/TAL1                          |                           |                                    |                                     |                                   | 0.162 |
| Positive/negative                 | 13/59                     | 2/14                               | 3/26                                | 8/19                              |       |
| TCR                               |                           |                                    |                                     |                                   | 0.364 |
| Positive/negative                 | 14/58                     | 4/12                               | 7/22                                | 3/24                              |       |
| WT1                               |                           |                                    |                                     |                                   | 0.288 |
| Positive/negative                 | 40/32                     | 11/5                               | 17/12                               | 12/15                             |       |
| CNSL at Initial Diagnosis         |                           |                                    |                                     |                                   | 0.261 |
| Yes/No                            | 4/70                      | 1/15                               | 3/28                                | 0/27                              |       |
| Chemotherapy regimen              |                           |                                    |                                     |                                   | 0.482 |
| CCLG-ALL-2008                     | 37(50%)                   | 7(43.8%)                           | 14(45.2%)                           | 16(59.3%)                         |       |
| Modified BFM protocol             | 37(50%)                   | 9(56.2%)                           | 17(54.8%)                           | 11(40.7%)                         |       |
| CR after IT                       | 66(89.2%)                 | 16(100%)                           | 28(90.3%)                           | 22(81.5%)                         | 0.211 |
**Follow-up Time (Months)**

| Median (range) | 51.2 (22.1-99.3) | 48.1 (34.0-88.7) | 51.8 (22.1-92.3) | 54.6 (22.2-99.3) | 0.592 |

ETP = early T-cell precursor. CNSL = central nervous system leukemia. IT = induction therapy.

**Early treatment response**

Sixty-six patients (89.2%) achieved CR at the end of induction chemotherapy, and 74 patients (100%) eventually achieved CR. Early T-cell precursor (ETP) was a risk factor related to CR after induction chemotherapy ($P = 0.000$). Other clinical characteristics such as sex, age, WBC count, $SIL/TAL1$ transcript, $TCR$ positive, $WT1$ positive and central nervous system leukemia (CNSL) at initial diagnosis, had no influence for early treatment response (Table 2).

**Table 2** Factors affecting early treatment response at diagnosis
| Factors                        | CR/ALL | Chi-square test | P   |
|-------------------------------|--------|-----------------|-----|
| Age, yr                       |        |                 |     |
| <10                           | 26/29  |                 | 0.011 | 1.000 |
| ≥10                           | 40/45  |                 |     |
| Sex                           |        |                 |     |
| Male                          | 48/52  |                 | 1.764 | 0.227 |
| Female                        | 18/22  |                 |     |
| WBC count, ×10⁹/L             |        |                 |     |
| <100                          | 37/44  |                 | 2.926 | 0.132 |
| ≥100                          | 29/30  |                 |     |
| ETP                           |        |                 |     |
| Yes                           | 6/13   |                 | 28.856 | 0.000 |
| No                            | 57/58  |                 |     |
| SIL/TAL1                      |        |                 |     |
| Negative                      | 51/59  |                 | 1.804 | 0.473 |
| Positive                      | 13/13  |                 |     |
| TCR                           |        |                 |     |
| Negative                      | 50/58  |                 | 2.038 | 0.476 |
| Positive                      | 14/14  |                 |     |
| WT1                           |        |                 |     |
| Negative                      | 30/32  |                 | 1.596 | 0.433 |
| Positive                      | 34/40  |                 |     |
| CNSL at Initial Diagnosis     |        |                 |     |
| Yes                           | 4/4    |                 | 0.513 | 1.000 |
| No                            | 62/70  |                 |     |
| Chemotherapy regimen          |        |                 |     |
| CCLG-ALL-2008                 | 32/37  |                 |     |
| Modified BFM protocol         | 34/37  |                 |     |
Early treatment response indicates the response at the end of induction therapy.

**Outcomes**

The study process is detailed in Fig. 1. Low-risk chemotherapy, high-risk chemotherapy, and high-risk transplant cohorts included 16, 31 and 27 patients respectively. There are no statistical difference for baseline characteristics among the three cohorts (Table 1).

27 patients were included in the high-risk transplant cohort, 23 received haplo-HSCT and 4 with matched sibling donor. Three of 27 transplant recipients were MRD-positive before allo-HSCT, and the remaining 24 patients were MRD-negative before allo-HSCT. The median time between diagnosis and transplant was 6.4 months (range, 3.4–15.6).

18 patients (24.3%) relapsed: 1 (6.3%) in the low-risk chemotherapy cohort, 14 (45.2%) in the high-risk chemotherapy cohort, and 3 (11.1%) in the high-risk transplant cohort. The median time of continuous complete remission was 11.55 months (range, 3.9–26.6) in the high-risk chemotherapy cohort and 12.4 months (range, 8–26.5) in the high-risk transplant cohort. 15 patients had hematologic relapse and 3 patients had extramedullary leukemia relapse. 19 patients had re-emergent MRD and the median time of MRD re-emergence was 7.9 months (range, 2.2–25.5). 20 patients had died and the median follow-up time was 15.75 months (range, 8.2–59.9). 16 patients died of relapse (13 in the high-risk chemotherapy cohort and 3 (haplo-HSCT) in the high-risk transplant cohort), 3 (haploidentical) patients died of transplant-related complications, and 1 patient died of severe pneumonia.

The 5-year OS was 70.2%±6.0% in all 74 patients, 100% in the low-risk chemotherapy cohort, and 51.2%±10% in the high-risk chemotherapy cohort \((P = 0.003)\) (Fig. 2A). The 5-year EFS was 67.8%±6.0% in all patients, 93.8%±6.1% in the low-risk chemotherapy cohort, and 48.4%±9.8% in the high-risk chemotherapy cohort \((P = 0.01)\) (Fig. 2B). The 5-year CIR was 24.7%±0.3% in the overall cohort, 6.3%±0.4% in the low-risk chemotherapy cohort, and 45.5%±0.8% in the high-risk chemotherapy cohort \((P = 0.043)\) (Fig. 3A). The 5-year OS, EFS, and CIR were 77.0%±8.3%, 77.0%±8.3%, and 11.9%±0.4% for the high-risk transplant cohort, respectively. When compared to the high-risk chemotherapy cohort, the P values were 0.084, 0.041, and 0.011, respectively (Fig. 2C, 2D, 3B). We also compared the prognosis of 24 patients in the high-risk transplant cohort who were CR1 and MRD-negative before allo-HSCT with the high-risk chemotherapy cohort (5-year OS: 83.3%±7.6% vs. 51.2%±10%, \(P = 0.04\); 5-year EFS: 83.3%±7.6% vs. 48.4%±9.8%, \(P = 0.018\); 5-year CIR: 4.2%±0.2% vs. 45.5%±0.8%, \(P = 0.014\)) (Fig. 2E, 2F, 3C). The prognosis of haplo-HSCT recipients who were CR1 and MRD negative before HSCT in the high-risk transplant cohort were compared to the high-risk chemotherapy cohort (5-year OS: 80.0%±8.9% vs. 51.2%±10%, \(P = 0.093\); 5-year EFS: 80.0%±8.9% vs. 48.4%±9.8%, \(P = 0.047\); 5-year CIR: 13.9%±0.6% vs. 45.5%±0.8%, \(P = 0.022\)).

**Factors related to OS, EFS, and CIR**

The univariate analysis of factors for OS, EFS, and CIR are shown in Table 3. MRD re-emergence and initial WBC count were risk factors for OS, EFS, and CIR. Chemotherapy regimen and age significantly
influenced OS and EFS, while transplant significantly influenced CIR. Multivariate analysis revealed that MRD re-emergence was an independent risk factor for OS, EFS, and CIR, age was an independent risk factor for OS and EFS, and initial WBC count was an independent risk factor for EFS and CIR (Table 4).

Table 3 Univariate analysis of factors associated with long-term prognosis in all 74 T-ALL patients.
| Factors          | No. of Cases | 5-Year OS(%) | P     | 5-Year EFS(%) | P     | 5-Year CIR(%) | P     |
|------------------|--------------|--------------|-------|---------------|-------|---------------|-------|
| Age, yr          |              |              |       |               |       |               |       |
| <10              | 29           | 89.5±5.7     | 0.013 | 82.6±7.1      | 0.080 | 17.4±0.5      | 0.26  |
| ≥10              | 45           | 59.2±8.0     |       | 59.5±7.9      |       | 29.5±0.5      |       |
| Sex              |              |              |       |               |       |               |       |
| Male             | 52           | 71.1±7.5     | 0.655 | 69.5±7.5      | 0.451 | 21.7±0.3      | 0.37  |
| Female           | 22           | 68.2±9.9     |       | 63.6±10.3     |       | 31.8±1.0      |       |
| WBC, ×10⁹/L      |              |              |       |               |       |               |       |
| <100             | 44           | 75.7±7.7     | 0.090 | 76.0±7.6      | 0.015 | 14.0±0.3      | 0.0064|
| ≥100             | 30           | 62.8±8.9     |       | 56.3±9.1      |       | 40.4±0.9      |       |
| Hemoglobin, g/L  |              |              |       |               |       |               |       |
| <100             | 25           | 80.0±8.0     | 0.445 | 76.0±8.5      | 0.609 | 20.0±0.7      | 0.73  |
| ≥100             | 43           | 65.7±8.3     |       | 63.9±8.2      |       | 26.5±0.5      |       |
| Platelet count, ×10⁹/L |          |              |       |               |       |               |       |
| <50              | 29           | 68.4±8.7     | 0.345 | 65.1±8.9      | 0.327 | 24.5±0.7      | 0.81  |
| ≥50              | 40           | 73.7±8.0     |       | 71.9±8.0      |       | 23.0±0.5      |       |
| ETP              |              |              |       |               |       |               |       |
| Yes              | 13           | 50.8±22.2    | 0.846 | 50.8±22.2     | 0.924 | 16.2±1.2      | 0.36  |
| No               | 58           | 73.7±5.8     |       | 70.3±6.1      |       | 26.2±0.3      |       |
| SIL/TAL1         |              |              |       |               |       |               |       |
| Negative         | 59           | 68.9±7.2     | 0.829 | 66.0±7.2      | 0.703 | 24.2±0.3      | 0.97  |
| Positive         | 13           | 76.9±11.7    |       | 76.9±11.7     |       | 23.1±1.5      |       |
| TCR              |              |              |       |               |       |               |       |
| Negative         | 58           | 71.8±7.2     | 0.587 | 68.9±7.2      | 0.686 | 22.8±0.3      | 0.64  |
| Positive         | 14           | 63.5±13.1    |       | 63.5±13.1     |       | 29.4±1.7      |       |
| WT1              |              |              |       |               |       |               |       |
| Negative         | 32           | 68.5±8.3     | 0.538 | 62.2±8.6      | 0.275 | 28.5±0.7      | 0.39  |
|                      | Positive | CNSL at Initial Diagnosis | CR after IT | MRD after IT | MRD at 3 months | MRD re-emergence | Chemotherapy regimen | Transplant |
|----------------------|----------|---------------------------|-------------|--------------|----------------|------------------|---------------------|------------|
|                      |          |                           | Yes         |                |                |                  |                     |            |
|                      |          | 4                         | 50.0±25.0   | 0.183         | 50.0±25.0      | 50.0±9.0         | 0.19                |            |
|                      |          | No                        | 71.3±6.2    | 73.4±8.4      | 68.8±6.2       | 23.3±0.3         |                     |            |
|                      |          |                           | Yes         |                |                |                  |                     |            |
|                      |          | 66                        | 73.3±6.1    | 0.105         | 70.5±6.2       | 23.0±0.3         | 0.36                |            |
|                      |          | No                        | 46.9±18.7   | 70.5±6.2      | 23.0±0.3       | 0.6±4.3          |                     |            |
|                      |          |                           | Negative    |                |                |                  |                     |            |
|                      |          | 55                        | 71.5±7.0    | 0.816         | 68.2±7.0       | 25.7±0.4         | 0.59                |            |
|                      |          | Positive                  | 68.8±11.6   | 68.8±11.6     | 18.8±1.0       | 0.8±1.0          |                     |            |
|                      |          |                           | Negative    |                |                |                  |                     |            |
|                      |          | 63                        | 73.4±6.4    | 0.163         | 70.4±6.5       | 22.5±0.3         | 0.53                |            |
|                      |          | Positive                  | 60.0±15.5   | 60.0±15.5     | 30.0±2.4       | 0.8±2.4          |                     |            |
|                      |          |                           | Yes         |                |                |                  |                     |            |
|                      |          | 19                        | 46.8±11.6   | 0.005         | 42.1±11.3      | 57.9±1.4         | 0.0041              |            |
|                      |          | No                        | 78.2±6.9    | 76.5±7.0      | 12.9±0.2       | 0.8±0.2          |                     |            |
|                      |          |                           | CCLG-ALL-2008 |              | 82.4±6.6     | 80.3±6.7         | 0.046               | 0.272      |
|                      |          | Modified BFM protocol     | 37          | 60.1±8.6     | 57.6±8.6       | 32.5±0.6         |                     |            |
|                      |          |                           | Yes         |                |                |                  |                     |            |
|                      |          | 27                        | 77.0±8.3    | 77.0±8.3      | 11.9±0.4       | 0.8±0.4          | 0.063               |            |
|                      |          | No                        | 66.1±8.3    | 62.3±8.3      | 32.0±0.5       | 0.8±0.5          |                     |            |

**Table 4** Multivariate analysis of factors associated with long-term prognosis in all 74 T-ALL patients.
| Variable                | OS HR (95% CI) | P   | EFS HR (95% CI) | P   | CIR HR (95% CI) | P   |
|------------------------|----------------|------|-----------------|-----|-----------------|-----|
| Age ≥ 10 yr            | 5.025(1.463-17.26) | 0.010 | 2.859(1.044-7.824) | 0.041 |                 |     |
| WBC ≥ 100×10^9/L       | 1.836(0.746-4.520) | 0.186 | 2.570(1.086-6.081) | 0.032 | 3.742(1.5829-9.16) | 0.0039 |
| MRD re-emergence       | 2.925(1.175-7.280) | 0.021 | 3.323(1.379-8.007) | 0.007 | 5.910(2.1008-16.63) | 0.00076 |
| CCLG-ALL-2008          | 0.427(0.158-1.154) | 0.094 | 0.547(0.214-1.401) | 0.209 |                 |     |
| Transplant             |                 |      |                 |     | 0.292(0.0835-1.02) | 0.053 |

HR indicates hazard ratio.

Discussion

In recent years, high-dose and multi-agent chemotherapy regimens have improved the outcomes of childhood T-ALL. The 5-year OS and EFS of 74 enrolled patients were 70.2%±6.0% and 67.8%±6.0%, respectively, which is comparable to reports by other centers[2, 3, 5–8].

The rate of CR after induction chemotherapy was 89.2%, and ETP was a risk factor related to CR after induction chemotherapy (P = 0.000). The AIEOP centers’ study confirmed that ETP-ALL had poor early treatment response and ETP-ALL patients obtained favourable outcome due to application of cyclophosphamide, 6-mercaptopurine, and ara-C[30]. In the COG AALL0434 study, 1144 patients were included and divided into three groups (ETP, near-ETP, and non-ETP). There are no statistical difference of 5-year OS and EFS among the three groups which showed a lack of significance of the ETP immunophenotype in pediatric T-ALL[25].

The prognosis of HR T-ALL remains unsatisfactory[9–12]. A risk-stratified approach to treat childhood T-ALL is warranted. In childhood ALL, age, WBC, and response to treatment are independent risk factors. However, the prognostic factors are different between B-ALL and T-ALL[26]. Herein, according to existing literature, we considered CR after induction therapy, MRD at 3 months, MRD re-emergence, or age ≥ 10 years as the hierarchical criteria[1, 2, 11, 23–26].

Patients with BM leukemic blasts > 25% after induction chemotherapy, those older than 10 years, or those with T-ALL were considered to be at particular risk[23]. Failure of induction therapy is rare in pediatric ALL (< 2% of patients), but may have a worse outcome[23, 24]. In our study, eight patients did not achieve CR at the end of induction chemotherapy, and four patients eventually died (three patients died of relapse and one died of intracranial hemorrhage).
Children with T-ALL have poorer tolerance to chemotherapy and have increased extramedullary relapse as a result of that they are generally older than children with B-ALL. This indicates that older age at presentation may lead a worse prognosis for patients with T-ALL[2]. In this study, age ≥ 10 years was an independent risk factor affecting 5-year OS and EFS, indicating that children older than 10 years of age have worse prognosis and are more likely to experience relapse. In the univariate analysis, the P value of age ≥ 10 years for EFS showed a downward trend that was not statistically significant, indicating that patients over 10 years of age may have poorer tolerance to chemotherapy and are more likely to experience treatment complications.

Initial WBC count is an important factor affecting ALL prognosis. In successive EORTC-CLG 58881 and 58951 trials, high-risk T-ALL patients were identified based on WBC count at presentation, CNS-positivity, and treatment response[6]. However in the UK trial, UKALL 2003, EFS was inversely related to WBC for B-ALL (P< 0.001) but not for T-ALL[31]. The Nordic Society of Pediatric Hematology and Oncology[31] and COG[32] also reported that initial WBC count was not a risk factor for T-ALL patients. In this study, high initial WBC count (WBC ≥ 100×10^9/L) was an independent risk factor affecting the 5-year EFS and CIR, indicating that children with a high initial WBC count may be at greater risk of relapse. The 5-year OS was unaffected by this factor, possibly owing to the application of intensive combination chemotherapy and bone marrow transplantation.

In childhood T-ALL, genetic subtypes such as SIL/TAL1 and t(v; 11q23)/MLL-rearranged are not meaningful, but MRD is a significant factor related to long-term outcomes in most cooperative group studies[1, 2]. Improved risk stratification eliminated the previous independent prognostic significance of gender and CNSL, whereas MRD level after induction therapy emerged as a risk stratifying feature[33]. A large percentage of childhood T-ALL patients have detectable MRD after induction chemotherapy, however, they could have a favourable outcomes if MRD converts to negative at post-consolidation[11]. In the AIEOP-BFM 2000 trial, the 7-year EFS of childhood T-ALL patients with positive MRD after induction and MRD converting to negative at day 78 was 81%. Conversely, T-ALL patients who were MRD-positive at day 78 had a relatively high 7-year CIR of 45% and were considered for HSCT at CR1[1, 11, 25, 26]. In this study, MRD positivity at 3 months was not an independent risk factor possibly due to the small sample size and the application of allo-HSCT. Furthermore, 10 patients had detected MRD at 3 months. Four patients chose chemotherapy, but three eventually died of relapse. Six patients chose allo-HSCT, but only one died of multiple organ dysfunction failure (MODF). MRD re-emergence was an independent risk factor affecting 5-year OS, EFS, and CIR, indicating that patients with MRD re-emergence during treatment had a relatively high relapse risk which seriously affected the prognosis.

Although intensive combination chemotherapy regimens are now widely used, allo-HSCT is still valuable for treatment of pediatric T-ALL. allo-HSCT should be strongly recommended for childhood T-ALL patients with positive MRD after consolidation[1]. It is suggested for patients to undergo allo-HSCT in condition of continuous CR and low-level MRD (United States<0.1%, United Kingdom<0.01%)[1, 11, 34]. In a study, childhood T-ALL patients older than 6 years who received allo-HSCT had a favourable survival compared to those received chemotherapy (5-year EFS of 40–45% vs. 26%)[24]. The German ALL-BFM 90 and 95
studies reported that 5-year DFS was 67% in the allo-HSCT group compared to 42% in the chemotherapy group[9]. In the AIEOP ALL 2000 study, children with T-ALL seemingly benefitted from allo-HSCT with a 5-year DFS of 59.7%[15]. A prospective study showed that the 5-year DFS rate was 62.2% in childhood T-ALL patients that were assigned related donor transplantation[16]. In a previous study at our institution, 35 HR childhood T-ALL patients received haplo-HSCT in CR1, and the 3-year LFS and CIR was 65.7% and 19.8% respectively[14]. Only a portion of T-ALL patients required allo-HSCT for cure. In this study, the 5-year OS, EFS, and CIR of the low-risk chemotherapy cohort were 100%, 93.8%±6.1%, and 6.3%±0.4% respectively, with the therapeutic effect exceeding the international level. Patients in high-risk chemotherapy cohort had a significantly worse outcomes that the 5-year OS, EFS, and CIR were 51.2%±10%, 48.4%±9.8%, and 45.5%±0.8%. The P values were 0.003, 0.01, and 0.043 respectively when compared to the low-risk chemotherapy cohort. This demonstrated good risk stratification of patients in this cohort. More importantly, the 5-year OS, EFS, and CIR were 77.0%±8.3%, 77.0%±8.3%, and 11.9%±0.4% respectively, for the high-risk transplant cohort. The therapeutic effect exceeded the level of our previous institutional study, which may be due to the improvement of transplantation technology. When compared to the high-risk chemotherapy cohort, the P values were 0.084, 0.041, and 0.011 respectively, validating that allo-HSCT was an effective strategy to reduce relapse and had the tendency to improve long-term survival in childhood HR T-ALL in CR1. We also compared the prognosis of 24 patients in the high-risk transplant cohort who were CR1 and MRD-negative before allo-HSCT versus the high-risk chemotherapy cohort. Patients in the high-risk group in CR1 with undetectable MRD before allo-HSCT had better outcomes compared to patients with detectable MRD before allo-HSCT. When the prognosis of haplo-HSCT recipients who were CR1 and MRD-negative before HSCT in the high-risk transplant cohort was compared to the high-risk chemotherapy cohort, haplo-HSCT tended to improve long-term survival and reduce relapse.

In previous international studies, conditioning regimen was usually based on TBI[9, 15, 16]. However, the associated side effects were significant. Recently, allo-HSCT without TBI has been proven effective for childhood ALL[35]. It has been demonstrated that central nervous system relapse of childhood ALL could be effectively prevented by risk-adjusted chemotherapy without cranial radiotherapy[26, 36]. Here, patients receiving allo-HSCT with a TBI-free, Bu-based conditioning regimen had a excellent outcomes with a 5-year OS of 77.0%±8.3% and a low 5-year CIR rate of 11.9%±0.4%.

However, this study is limited because it is a nonrandomized retrospective study with a small sample size in a single-center. In addition, two different chemotherapy regimens were applied to patients which may cause bias, however, there were no statistical difference for long-term survival between patients with those two regimens.

**Conclusion**

The results of our study indicate that allo-HSCT (especially haplo-HSCT) could be a feasible option for children with high-risk T-ALL in CR1. It could improve long-term survival and reduce the risk of relapse for
those patients. However, the results should be further confirmed by prospective, multicentre, randomized controlled clinical trials.

**Abbreviations**

allo-HSCT: Allogeneic hematopoietic stem cell transplantation; haplo-HSCT: haploidentical HSCT; HR: High-risk; T-ALL: T-cell acute lymphoblastic leukemia; CR1: First complete remission; OS: Overall survival; EFS: Event-free survival; CIR: Cumulative incidence of relapse; DFS: Disease-free survival; LFS: leukemia-free survival; MRD: Minimal residual disease; BFM: Berlin-Frankfurt-Munster; CCLG: Chinese Children Leukemia Group; BM: Bone marrow; FCM: Flow cytometry; TBI: total body irradiation; Bu-Cy: busulfan-cyclophosphamide; Me-CCNU: methyl-N-(2-chloroethyl)-N-cyclohexyl-N-nitrosourea; ATG: anti-thymocyte immunoglobulin; G-CSF: Granulocyte colony-stimulating factor; PBSC: peripheral blood stem cells; MTX: methotrexate; MMF: mycophenolate mofetil; CsA: cyclosporine A; GVHD: graft versus host disease; ETP: early T-cell precursor; CNSL: central nervous system leukemia; IT: induction therapy.

**Declarations**

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**Authors’ contributions**

Yong-zhan Zhang and Lu Bai analysed data and wrote the manuscript. Jun Wu, Ying-xi Zuo, Yue-ping Jia and Yi-fei Cheng managed patients and performed follow-up. Ai-dong Lu, Yu Wang, Xiao-hui Zhang, Lan-ping Xu and Xiao-jun Huang reviewed and revised this manuscript. Le-ping Zhang and Yi-fei Cheng designed the research. All authors approved of the submission of final manuscript.

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**Availability of data and materials**

The datasets supporting the conclusions of this article are included within the article.

**Ethics approval and consent to participate**

The Ethics Committee of Peking University People’s Hospital approved the collection, analysis, and publication of the data. Informed consent was waived by the Ethics Committee of Peking University People’s Hospital due to the retrospective nature of the study. All methods of this study were carried out in accordance with the Declaration of Helsinki.
Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures
Figure 1

Diagram of all patients included in the study

Figure 2

Kaplan-Meier estimates of 5-year outcomes in the three cohorts. (A) OS in low-risk chemotherapy cohort versus high-risk chemotherapy cohort, (B) EFS in low-risk chemotherapy cohort versus high-risk...
Figure 3

Kaplan-Meier estimates of 5-year outcomes in the three cohorts. (A) CIR in low-risk chemotherapy cohort versus high-risk chemotherapy cohort, (B) CIR in high-risk chemotherapy cohort versus high-risk transplant cohort, (C) CIR in high-risk chemotherapy cohort versus 24 patients of high-risk transplant cohort who were CR1 and MRD negative before allo-HSCT.