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

Purpose

The role of hematopoietic stem cell transplantation (HSCT) for children with high-risk (HR) T-cell acute lymphoblastic leukemia (T-ALL) in first complete remission (CR1) is still under critical discussion. This study explored the hierarchical criteria, prognostic factors of childhood T-ALL, and the role of HSCT, especially haplo-HSCT, for children with HR T-ALL in CR1.

Methods

Seventy-four 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=24).

Results

Patient prognosis in the high-risk chemotherapy cohort was significantly inferior to the low-risk chemotherapy cohort (5-year overall survival (OS): $51.2\% \pm 10\%$ vs. 100% , $P = 0.003$; 5-year event-free survival (EFS): $48.4\% \pm 9.8\%$ vs. $93.8\% \pm 6.1\%$, $P = 0.01$; 5-year cumulative incidence of relapse (CIR): $45.5\% \pm 0.8\%$ vs. $6.3\% \pm 0.4\%$, $P = 0.043$). The 5-year OS, EFS, and CIR of the high-risk transplant cohort were $77.0\% \pm 8.3\%$, $77.0\% \pm 8.3\%$, and $11.9\% \pm 0.4\%$, respectively. When compared to the high-risk chemotherapy cohort, the P values were 0.084, 0.041, and 0.011, respectively. Minimal residual disease (MRD) re-emergence, initial white blood cell (WBC) count, and age ≥ 10 years were independent risk factors for prognosis.

Conclusions

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

Introduction

T-cell acute lymphoblastic leukemia, an aggressive malignancy associated with poor prognosis, accounts for 10–15% of all pediatric ALL cases (Pui, et al 2008, Raetz and Teachey 2016, Teachey and O'Connor 2020, Teachey and Pui 2019). With the advent of various intensive combination chemotherapy regimens in recent years, the 5-year OS and EFS rates have significantly increased to 71.9%-91.4% and 64%-87.8%, respectively for children with T-ALL (Asselin, et al 2011, Hofmans, et al 2019, Karrman and Johansson 2017, Raetz and Teachey 2016, Teachey and Pui 2019, Winter, et al 2018). However, patients with HR childhood T-ALL have shown unsatisfactory long-term OS and EFS of less than 50% (Dunsmore, et al 2012, Schrappe, et al 2011, Schrauder, et al 2006, Willemse, et al 2002). Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is sometimes recommended for children at CR1 showing HR characteristics and often recommended for patients at second or later CR (Hochberg, et al 2013). But children with T-ALL at CR2 or later CR had significantly worse prognosis even if they were treated with

HSCT. In the past study in our institution, the 3-year LFS for children with T-ALL at CR2 or later CR was only 26.0% and 3-year CIR was 56.7%(Xu, et al 2016). Few studies have demonstrated that the dismal prognosis of HR childhood T-ALL could be improved with allo-HSCT(Balduzzi, et al 2005, Conter, et al 2014, Schrauder, et al 2006). 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 HSCT in CR1 was 67%, and patients who treated with chemotherapy alone were 47% and 42% respectively(Schrauder, et al 2006). Therefore, a risk-stratified approach to treat childhood T-ALL is warranted. In recent years, haploidentical hematopoietic stem cell transplantation (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(Huang, et al 2006, Liu, et al 2008, Liu, et al 2013, Wang, et al 2012, Xu, et al 2016). 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 HSCT, especially haplo-HSCT, for children with HR childhood T-ALL in CR1.

Materials And 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(Xue, et al 2019) or the Chinese Children Leukemia Group (CCLG)-ALL 2008 protocol(Cui, et al 2018). 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. The study was in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Peking University People's Hospital. Informed consent was obtained from patients and/or their guardians and donors.

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)(Merli, et al 2019, Schrappe, et al 2012); (2) MRD level $\geq 1 \times 10^{-4}$ in bone marrow aspirate three months after initial diagnosis(Hefazi and Litzow 2018, Patrick and Vora 2015, Schrappe, et al 2011, Teachey and O'Connor 2020); (3) age ≥ 10 years(Merli, et al 2019, Teachey and Pui 2019) and (4) re-emergent MRD.

Definitions and evaluations

Complete remission was defined as bone marrow (BM) leukemic blasts < 5% with regenerating hematopoiesis (platelet count > $100 \times 10^9/\text{L}$, neutrophils > $1 \times 10^9/\text{L}$) and no localised leukemic infiltrates. MRD of bone marrow was tested by flow cytometry (FCM) and/or quantitative PCR (Cheng, et al 2013, Parekh, et al 2015, Pui, et al 2017). MRD positivity was defined as $\text{FCM} \geq 1 \times 10^{-4}$, including positive detection of other mutated genes (*SIL/TAL 1*, *t(v; 11q23)*/*MLL*-rearranged). Relapse was defined as recurrence of $\geq 5\%$ BM leukemic blasts and/or localized leukemic infiltrates at any site.

Overall survival (OS) was defined as time from diagnosis to death from any cause or the the date of final follow-up. Event-free survival (EFS) was defined as time from diagnosis to relapse, second tumor, death or the date of final follow-up. The cumulative incidence of relapse (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 regiment for MSD transplants was a modified busulfan-cyclophosphamide (Bu-Cy) conditioning regiment that included hydroxyurea (80 mg/kg/day, p.o., on day - 10); cytarabine ($2 \text{ g/m}^2/\text{day}$, i.v., on day - 9); Bu (3.2 mg/kg/day , i.v., on days - 8 to -6); Cy ($1.8 \text{ g/m}^2/\text{day}$, 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 regiment for haplo-transplants consisted of cytarabine ($4 \text{ g/m}^2/\text{day}$, 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 (Huang, et al 2006, Liu, et al 2008, Liu, et al 2013, Wang, et al 2012, Xu, et al 2016).

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 $P < 0.05$ 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, $\times 10^9/L$					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, $\times 10^9/L$					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%)	
ETP, early T-cell precursor. CNSL, central nervous system leukaemia. IT, induction therapy.					

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
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 leukaemia. 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/TAL 1* 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	<i>P</i>
Age, yr		0.011	1.000
<10	26/29		
≥10	40/45		
Sex		1.764	0.227
Male	48/52		
Female	18/22		
WBC count, ×10 ⁹ /L		2.926	0.132
<100	37/44		
≥100	29/30		
ETP		28.856	0.000
Yes	6/13		
No	57/58		
<i>SIL/TAL1</i>		1.804	0.473
Negative	51/59		
Positive	13/13		
<i>TCR</i>		2.038	0.476
Negative	50/58		
Positive	14/14		
<i>WT1</i>		1.596	0.433
Negative	30/32		
Positive	34/40		
CNSL at Initial Diagnosis		0.513	1.000
Yes	4/4		
No	62/70		
Chemotherapy regimen		0.561	0.711

Early treatment response indicates the response at the end of induction therapy.

Factors	CR/ALL	Chi-square test	<i>P</i>
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 HSCT, and the remaining 24 patients were MRD-negative before 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 (haplo-identical) 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. (Figs. 2C, 2D, 3B). We also compared the prognosis of 24 patients in the high-risk transplant cohort who were CR1 and MRD-negative before 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%, $P=0.014$) (Figs. 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, ×10 ⁹ /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, ×10 ⁹ /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							

Factors	No. of Cases	5-Year OS(%)	P	5-Year EFS(%)	P	5-Year CIR(%)	P
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	40	73.1 ± 8.4		73.4 ± 8.4		20.5 ± 0.4	
CNSL at Initial Diagnosis							
Yes	4	50.0 ± 25.0	0.183	50.0 ± 25.0	0.294	50.0 ± 9.0	0.19
No	70	71.3 ± 6.2		68.8 ± 6.2		23.3 ± 0.3	
CR after IT							
Yes	66	73.3 ± 6.1	0.105	70.5 ± 6.2	0.164	23.0 ± 0.3	0.36
No	8	46.9 ± 18.7		46.9 ± 18.7		40.6 ± 4.3	
MRD after IT							
Negative	55	71.5 ± 7.0	0.816	68.2 ± 7.0	0.978	25.7 ± 0.4	0.59
Positive	16	68.8 ± 11.6		68.8 ± 11.6		18.8 ± 1.0	
MRD at 3 months							
Negative	63	73.4 ± 6.4	0.163	70.4 ± 6.5	0.299	22.5 ± 0.3	0.53
Positive	10	60.0 ± 15.5		60.0 ± 15.5		30.0 ± 2.4	

Factors	No. of Cases	5-Year OS(%)	P	5-Year EFS(%)	P	5-Year CIR(%)	P
MRD re-emergence							
Yes	19	46.8 ± 11.6	0.005	42.1 ± 11.3	0.002	57.9 ± 1.4	0.00041
No	55	78.2 ± 6.9		76.5 ± 7.0		12.9 ± 0.2	
Chemotherapy regimen							
CCLG-ALL-2008	37	82.4 ± 6.6	0.046	80.3 ± 6.7	0.060	17.0 ± 0.4	0.11
Modified BFM protocol	37	60.1 ± 8.6		57.6 ± 8.6		32.5 ± 0.6	
Transplant							
Yes	27	77.0 ± 8.3	0.505	77.0 ± 8.3	0.272	11.9 ± 0.4	0.063
No	47	66.1 ± 8.3		62.3 ± 8.3		32.0 ± 0.5	

Table 4
Multivariate analysis of factors associated with long-term prognosis in all 74 T-ALL patients

	OS		EFS		CIR	
Variable	HR (95% CI)	P	HR (95% CI)	P	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 $70.2\% \pm 6.0\%$ and $67.8\% \pm 6.0\%$, respectively, which is comparable to reports by other centers (Asselin, et al 2011, Hofmans, et al 2019, Karrman and Johansson 2017, Raetz and Teachey 2016, Teachey and Pui 2019, Winter, et al 2018).

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 (Conter, et al 2016). 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 (Hefazi and Litzow 2018).

The prognosis of HR T-ALL remains unsatisfactory (Dunsmore, et al 2012, Schrappe, et al 2011, Schrauder, et al 2006, Willemse, et al 2002). 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 (Patrick and Vora 2015). 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 (Hefazi and Litzow 2018, Merli, et al 2019, Patrick and Vora 2015, Schrappe, et al 2012, Schrappe, et al 2011, Teachey and O'Connor 2020, Teachey and Pui 2019).

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 (Merli, et al 2019). Failure of induction therapy is rare in pediatric ALL ($< 2\%$ of patients), but may have a worse outcome (Merli, et al 2019, Schrappe, et al 2012). 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 (Teachey and Pui 2019). 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 (Hofmans, et al 2019). However in the UK trial, UKALL 2003, EFS was inversely related to WBC for B-ALL ($P < 0.001$) but not for T-ALL (Vaitkevicin, et al 2011). The Nordic Society of Pediatric Hematology and Oncology (Vaitkevicin, et al 2011) and COG (Hastings, et al 2015) also reported that initial WBC count was not a risk factor for T-ALL patients. In this study, high initial WBC

count ($\text{WBC} \geq 100 \times 10^9/\text{L}$) 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/TAL 1* 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 (Teachey and O'Connor 2020, Teachey and Pui 2019). 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 (Schmiegelow, et al 2010). 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 (Schrappe, et al 2011). 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 (Hefazi and Litzow 2018, Patrick and Vora 2015, Schrappe, et al 2011, Teachey and O'Connor 2020). 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 HSCT. Furthermore, 10 patients had detected MRD at 3 months. Four patients chose chemotherapy, but three eventually died of relapse. Six patients chose 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, HSCT is still valuable for treatment of pediatric T-ALL. HSCT should be strongly recommended for childhood T-ALL patients with positive MRD after consolidation (Teachey and O'Connor 2020). It is suggested for patients to undergo HSCT in condition of continuous CR and low-level MRD (United States $\leq 0.1\%$, United Kingdom $\leq 0.01\%$) (O'Connor, et al 2017, Schrappe, et al 2011, Teachey and O'Connor 2020). In a study, childhood T-ALL patients older than 6 years who received HSCT had a favourable survival compared to those received chemotherapy (5-year EFS of 40–45% vs. 26%) (Schrappe, et al 2012). The German ALL-BFM 90 and 95 studies reported that 5-year DFS was 67% in the HSCT group compared to 42% in the chemotherapy group (Schrauder, et al 2006). In the AIEOP ALL 2000 study, children with T-ALL seemingly benefitted from HSCT with a 5-year DFS of 59.7% (Conter, et al 2014). A prospective study showed that the 5-year DFS rate was 62.2% in childhood T-ALL patients that were assigned related donor transplantation (Balduzzi, et al 2005). 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 (Xu, et al 2016). Only a portion of T-ALL patients required HSCT for cure. In this study, the 5-year OS, EFS, and CIR of the low-risk chemotherapy cohort were 100%, $93.8\% \pm 6.1\%$, and $6.3\% \pm 0.4\%$ 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 $51.2\% \pm 10\%$, $48.4\% \pm 9.8\%$, and $45.5\% \pm 0.8\%$. 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 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 HSCT versus the high-risk chemotherapy cohort. Patients in the high-risk group in CR1 with undetectable MRD before HSCT had better outcomes compared to patients with detectable MRD before 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 (Balduzzi, et al 2005, Conter, et al 2014, Schrauder, et al 2006). However, the associated side effects were significant. Recently, HSCT without TBI has been proven effective for childhood ALL (Hamidieh, et al 2017). It has been demonstrated that central nervous system relapse of childhood ALL could be effectively prevented by risk-adjusted chemotherapy without cranial radiotherapy (Patrick and Vora 2015, Pui, et al 2009). Here, patients receiving HSCT with a TBI-free, Bu-based conditioning regimen had excellent outcomes with a 5-year OS of 77.0%±8.3% and a low 5-year CIR rate of 11.9%±0.4%.

In conclusion, HSCT (especially haplo-HSCT) without TBI may improve long-term prognosis for children with high-risk T-ALL in CR1. 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. The results should be further confirmed by prospective, multicentre, randomized controlled clinical trials.

Declarations

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Author 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 were the principal investigators and designed the research. All authors approved of the submission of final manuscript.

Compliance with ethical standards

Conflict of interest

None.

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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 chemotherapy cohort, (C) OS in high-risk chemotherapy cohort versus high-risk transplant cohort, (D) EFS in high-risk chemotherapy cohort versus high-risk transplant cohort, (E) OS in high-risk chemotherapy cohort versus 24 patients of high-risk transplant cohort who were CR1 and MRD negative before HSCT, (F) EFS in high-risk chemotherapy cohort versus 24 patients of high-risk transplant cohort who were CR1 and MRD negative before HSCT.

A

B

C

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 HSCT.