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Allogeneic Hematopoietic Stem Cell Transplantation, Especially Haploidentical, May Improve Long-Term Survival for High-Risk Pediatric Patients with Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia in the Tyrosine Kinase Inhibitor Era

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The role of allogeneic hematopoietic stem cell transplantation (allo-HSCT), particularly haploidentical (haplo)-HSCT, in pediatric patients with Philadelphia chromosome–positive (Ph+) acute lymphoblastic leukemia (ALL) in the tyrosine kinase inhibitor (TKI) era is unclear. This study aimed to identify prognostic factors and explore the role of haplo-HSCT in the treatment of Ph+ ALL in the TKI era. We analyzed clinical data of Ph+ ALL patients aged 1 to 18 years who received imatinib added to intensive chemotherapy at the start of induction therapy. Among the 68 patients who completed at least 2 consolidation cycles, 44 underwent transplantation (transplant arm) and 24 received continuous TKI with chemotherapy (nontransplant arm). At the 3-year follow-up the cumulative incidence of relapse (CIR), event-free survival (EFS), and overall survival (OS) were 23.5%, 73.4%, and 80.3%, respectively. Multivariate analysis showed that hematologic response (whether complete remission [CR] was achieved) at the induction end, *BCR-ABL* levels (whether major molecular response [MMR] was achieved) at 3 months, and transplantation were independent affecting factors for CIR, EFS, and OS. In the risk stratification analysis based on the first 2 prognostic factors mentioned above, no significant difference existed between the transplant and nontransplant arms for the probabilities of 3-year OS, EFS, and CIR in the standard-risk group (no poor prognostic factors). Meanwhile, OS, EFS, and CIR rates were significantly better in the transplant arm in the high-risk group (≥1 poor prognostic factor). Among the 44 patients in the transplant arm, 37 underwent haplo-HSCT. Achieving CR at the induction end, MMR at 3 months, and haplo-transplant were also independent favorable factors of CIR, EFS, and OS in the nontransplant and haplo-HSCT arms. Haplo-HSCT showed a significant survival advantage in the high-risk group only. Hematologic response at the induction end and *BCR-ABL* levels at 3 months are likely to be useful for identifying pediatric Ph+ ALL patients at a high risk of relapse in the TKI era. Children with Ph+ ALL in first CR may benefit from allo-HSCT, particularly those at high risk. Haplo-HSCT could achieve good long-term survival for pediatric Ph+ ALL. Thus, haplo-HSCT can be an alternative approach for high-risk Ph+ ALL patients.

INTRODUCTION

Philadelphia chromosome–positive (Ph+) acute lymphoblastic leukemia (ALL) occurs in 3% to 5% of patients with childhood ALL and is associated with dismal outcomes when treated with chemotherapy alone in the era before tyrosine kinase inhibitors (TKIs) [1]. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is often recommended because it results in a lower relapse rate [1-3]. Over the past decade an imatinib-incorporating regimen has been reported to increase complete remission (CR) and has resulted in promising outcomes similar to that of allo-HSCT in pediatric patients with Ph+ ALL [4-7]. The Children's Oncology Group conducted the first large prospective cohort study (AALL0031) of pediatric patients with Ph+ ALL treated with chemotherapy and TKI to assess the efficacy of increased exposure to imatinib combined with

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chemotherapy in 5 cohorts. In this study 44 children in cohort A5 (continuous imatinib from consolidation to the end of treatment) had a 3-year event-free survival (EFS) rate of 80%, and 28 patients in this cohort treated with chemotherapy plus imatinib continuously had a 5-year disease-free survival rate of 70%. Allo-HSCT did not show an advantage compared with chemotherapy plus imatinib [5, 6]. The major improvement achieved with TKIs in combination with chemotherapy challenges the central role of allo-SCT established in the preimatinib era. However, whether intensive chemotherapy plus TKIs could replace allo-HSCT for pediatric patients with Ph+ ALL remains unclear to date [8]. Contemporary trials have focused on defining the optimal use of chemotherapy, HSCT, and TKI in Ph+ ALL [9]. The French Acute Lymphoblastic Leukaemia Study Group [10] and the Spanish Paediatric Haematology Oncology Group (SHOP) [11] analyzed a series of prognostic factors in pediatric patients with Ph+ ALL and described a prognostic index that could discriminate a subgroup of patients with a better prognosis, for whom allo-HSCT may be omitted in the pre-TKI era. Therefore, it is also necessary to use a risk-stratified approach for treatment of childhood Ph+ ALL in the current TKI era.

In previous clinical studies, matched related and matched unrelated donors were used for HSCT. In China, because of the implementation of the family planning policy, haploidentical (haplo)-HSCT has become an important choice for many Ph+ ALL children when undergoing transplantation. However, there have been few reports on haplo-HSCT in children with Ph+ ALL. In our previous report we demonstrated the safety and efficacy of haplo-HSCT in the treatment of pediatric Ph+ ALL [12]. However, to the best of our knowledge, no study has compared the efficacy of haplo-HSCT and TKI-based chemotherapy in pediatric Ph+ ALL in the TKI era. Thus, this study aimed to identify the prognostic factors and explore the role of HSCT, particularly haplo-HSCT, in the treatment of Ph+ ALL children in different risk categories in the TKI era.

METHODS

Patient Eligibility

We collected data on the clinical characteristics and outcomes of pediatric patients (ie, those aged between 1 and 18 years) who were newly diagnosed with Ph+ ALL from 2010 to 2016. Ph+ ALL was diagnosed based on cytogenetic abnormalities and/or molecular studies of the *BCR-ABL* translocation, according to the World Health Organization diagnosis criteria [13]. All patients in the study received TKIs during induction therapy and were then nonrandomly divided to receive either the combination of TKIs and chemotherapy (nontransplant cohort) or transplant (transplant cohort; all performed during the first morphologic CR) based on their own preferences. This study was approved by the ethics committee of Peking University People's Hospital after written informed consent was obtained from patients or their parents/guardians for a prospective study randomizing the treatment regimens.

Tyrosine Kinase Inhibitors

Once a patient was diagnosed with Ph+ ALL (days 8 to 15 of induction therapy), imatinib mesylate (Novartis, Basel, Switzerland) was initiated at a dose of 260 to 340 mg/m^2/d. For patients who failed the treatment [14], were diagnosed with central nervous system leukemia (CNSL), or were imatinib resistant, a second-generation TKI, dasatinib (Bristol-Myers Squibb Company, Mount Vernon, America), was administered as a replacement at an initial dose of 50 mg/m^2/d, if the patient had no dasatinib-resistant *BCR-ABL* mutations, such as *T315I*, *V299L*, *T315A*, and *F317L/V/I/C*.

TKIs were continuously administered during induction, consolidation, and maintenance treatment for patients in the nontransplant cohort and were administered until initiation of the conditioning regimen of transplantation for patients in the transplant cohort. TKI administration after transplantation has been reported in previous literature [12,15,16]. TKIs were continuously administered for at least 12 months after HSCT. If grades III to IV myelosuppression or grades III to IV nonhematologic adverse reactions occurred during the use of TKIs, TKIs were suspended or the dose was reduced as necessary and then resumed on recovery.

Chemotherapy

All patients received at least 1 course of chemotherapy. They were randomly assigned to 2 different chemotherapy regimens: the Chinese children's protocol for ALL 2008 (CCLG-ALL) [17] or a modified ALL-Berlin-Frankfurt-Munster (BFM) protocol. The modified ALL-BFM protocol included a 5-drug prednisone-based induction (CODPL), followed by consolidation therapy with 2 cycles of reinduction block in between and then maintenance therapy (Table 1, Figure 1). The consolidation chemotherapy regimen comprised high-dose methotrexate with or without pegaspargase, high-dose cytarabine, and reinduction block (CODPL), which were given sequentially. Reinduction was performed every 6 months during the consolidation treatment. There were 15 rounds of high-dose methotrexate with or without pegaspargase and 3 rounds of high-dose cytarabine (Ara-c) during the entire consolidation treatment. The total doses of daunomycin (or idarubicin) and L-asparaginase were 400 mg/m^2 (or 100 mg/m^2) and 300,000 units, respectively. Moreover, the total course of treatment was 3 to 3.5 years. Prophylaxis for CNSL, intrathecal chemotherapy with methotrexate, Ara-c, and dexamethasone was administered 23 to 25 times to the patients in the nontransplant cohort and at least 6 times in the transplant cohort. Patients presenting with CNS disease received twice-weekly intrathecal chemotherapy until the cerebrospinal fluid normalized and then received once-weekly CNS therapy for 4 more doses.

Transplantation

After at least 2 rounds of TKI-based consolidation therapy, patients in first CR with either a matched sibling donor (MSD) or a haplo family donor underwent a myeloablative transplant according to their guardians' wishes. An unrelated cord blood (UCB) unit with a minimum of 4/6 HLA loci match transplantation was also considered as an alternative.

Conditioning regimens were administered as previously described [12,14,16,18]. In MSD transplants the conditioning regimen was a modified busulfan-cyclophosphamide regimen, including the following: hydroxyurea (80 mg/kg/d) p.o. on day −10, Ara-c (2 g/m^2/d) i.v. on day −9, busulfan (3.2 mg/kg/d) i.v. from days −8 to −6; cyclophosphamide (1.8 g/m^2/d) i.v. from days −5 to −4; and methyl-*N*-(2-chloroethyl)-*N*-cyclohexyl-*N*-nitrosourea (250 mg/kg/d) p.o. on day −3. In UCB and haplo-transplants the conditioning regimen was modified busulfan-cyclophosphamide combined with human antithymocyte immunoglobulin as follows: Ara-c (4 g/m^2/d) from days −10 to −9; busulfan, cyclophosphamide, and methyl-*N*-(2-chloroethyl)-*N*-cyclohexyl-*N*-nitrosourea (as described above); and human antithymocyte immunoglobulin (2.5 mg/kg/d; Sang Stat, Lyon, France) for 4 days from days −5 to −2. MSD and haplo-transplant recipients received granulocyte colony-stimulating factor–mobilized bone marrow cells plus peripheral blood stem cells and cyclosporine A (Bavaria, Novartis, Germany), mycophenolate mofetil (New Jersey, Roche, USA), short-term methotrexate as prophylaxis for acute graft-versus-host disease (aGVHD), whereas UCB transplant recipients received

Table 1
Modified ALL-BFM Protocol in our Institution

Induction and reinduction (CODPL)
VCR 1.5 mg/m^2 (max, 2m g) days 1, 8, 15, 22
CTX 1 g/m^2 days 1
DNR (or IDR) 40-60 mg/m^2 (or 8-10 mg/m^2) days 1, 8
L-asp 10,000 U/m^2 days 15, 17, 19, 21, 23, 25, 27, 29, 31, 33
DEX or Pred 10 mg/m^2 (max, 10 mg)or 60 mg/m^2 (max, 60 mg) days 1-28
Consolidation
HDMTX × 2
HDMTX 2.5-3.5 g/m^2 days 1, 22
VCR 1.5 mg/m^2 (max, 2 mg) days 1, 8, 15, 22
DNR (or IDR) 40-60 mg/m^2 (or 8-10 mg/m^2) days 8, 10
HDMTX
HDMTX 2.5-3.5 g/m^2 day 1
VCR 1.5 mg/m^2 (max, 2 mg) day 1
HDAra-C
HDAra-C 2 g/m^2 days 1-3
DNR (or IDR) 40-60 mg/m^2 (or 8-10 mg/m^2) days 2-3
IFO
IFO 1 g/m^2 days 1-5
VP-16 100 mg/m^2 days 3-5
VCR 1.5 mg/m^2 (max, 2 mg) day 1
Maintenance therapy
6-MP 50 mg/m^2 once a day
MTX 20 mg/m^2 once a week

DEX indicates dexamethasone; Pred, prednisone; VCR, vincristine; CTX, cyclophosphamide; DNR, daunomycin; IDR, idarubicin; L-asp, native *Escherichia coli* L-asparaginase; HDMTX, high-dose methotrexate; HDAra-C, high-dose cytarabine; IFO, ifosfamide; VP-16, etoposide; 6-MP, mercaptopurine.

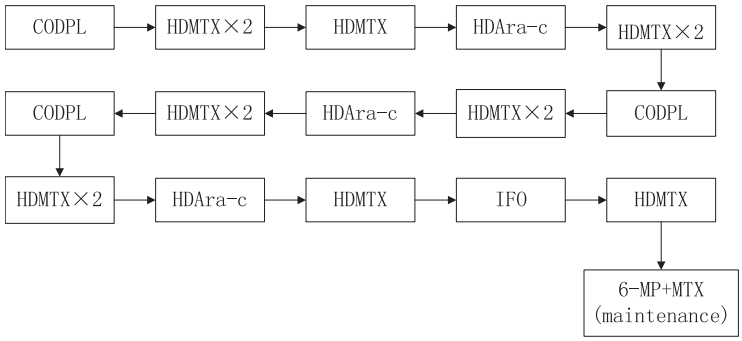

Figure 1. Flow chart of modified ALL-BFM protocol.

methylprednisolone instead of methotrexate. The stem cell for haplo-transplant was from unmanipulated marrow and did not involve CD34 selection process. Supportive care was given as described previously [18].

Minimal Residual Disease Assessment and Definitions

TaqMan-based, quantitative, real-time, reverse transcription PCR was used to assess the minimal residual disease (MRD) (levels of *BCR-ABL* transcripts), and the normalization ratio of the *BCR-ABL* transcript level was determined through comparison with the ABL transcript level, as previously reported [19]. CR was defined as M1 marrow (<5% blasts) with regenerating hematopoiesis and no localized leukemic infiltrates. Complete molecular response (CMR) was defined as negative expression of the *BCR-ABL* transcript. Major molecular response (MMR) was defined as ≥3-log reduction of the level of *BCR-ABL* transcript compared with the baseline at diagnosis (including CMR). Early treatment response was evaluated according to the rate of CR and MMR at induction end. Relapse was defined as recurrence of ≥5% lymphoblasts in bone marrow aspirates or extramedullary leukemia at any site. Treatment failure was defined once 1 of the following events occurred: no CR after a 4-week induction, >1 log increase of *BCR-ABL* during therapy, recurrence of *BCR-ABL* transcript after achieving a CMR, or hematologic relapse. The methodology for the detection of a *BCR-ABL* point mutation was described previously [14]. Ikaros family zinc finger protein 1 was detected in patients with available samples via multiplex fluorescent PCR [20].

Statistical Analysis

EFS was calculated from the date of diagnosis to the first event (remission failure, death for any reason in CR, relapse, or second malignancy) or the date of last follow-up. Overall survival (OS) was calculated from the date of diagnosis to death due to any cause. The cumulative incidence of relapse (CIR) was calculated from the date of CR to relapse. Nonrelapse mortality was defined as death without disease progression or relapse.

Table 2
Characteristics of Ph+ ALL Patients (N = 70)

Parameter	All Patients Cohort (N = 70)	*P**	Haplo-HSCT Cohort (n = 37)	Nontransplant Cohort (n = 24)	Transplant Cohort (n = 44)	*P*†
Age, yr		.016				.027
Median (range)	10 (1-17)		11 (5-17)	8 (1-16)	10.5 (1-17)	
<10	34		13	16	17	
≥10	36		24	8	27	
Sex, male/female	46/24	.942	25/12	16/8	30/14	.898
WBC count, $\times 10^9$/L		.930				.667
Median (range)	49.2 (2.0-481.2)		57.1 (2.1-481.2)	49.2 (2.0-425.6)	41.7 (2.1-481.2)	
<100	44 (62.9%)		22 (59.5%)	14 (58.3%)	28 (63.6%)	
≥100	26 (37.1%)		15 (40.5%)	10 (41.7%)	16 (36.4%)	
Hemoglobin, g/L		.074				.119
Median (range)	101.5 (31-156)		103 (38-156)	93 (52-139)	103 (38-156)	
Platelet count, $\times 10^9$/L		.181				.242
Median (range)	55.5 (4-399)		62 (8-399)	30.5 (4-383)	61 (8-399)	
CD13 and/or CD33		.674				.881
Positive/negative	33/37		19/18	11/13	21/23	
Ph+ chromosome		.352				.554
T (9;22) only	34 (60.7%)		17 (53.1%)	12 (66.7%)	21 (58.3%)	
Other abnormalities	22 (39.3%)		15 (46.9%)	6 (33.3%)	15 (41.7%)	
IM/ND	14					
BCR-ABL transcript		.751				1.000
P190/P210	55/15		28/9	19/5	35/9	
IKZF deletion	15 (48.4%)	1.000	9 (52.9%)	5 (50.0%)	9 (45.0%)	1.000
CR after IT	63 (90.0%)	.449	32 (86.5%)	23 (95.8%)	39 (88.6%)	.581
MMR after IT	31 (44.3%)	.793	16 (43.2%)	12 (50.0%)	19 (43.2%)	.619
MMR after 3 mo	44 (64.7%)	.234	27 (73.0%)	14 (58.3%)	30 (68.2%)	.417
CNS involvement		1.000				.924
Yes	4 (5.7%)		2 (5.4%)	2 (8.3%)	2 (4.5%)	
No	66 (94.3%)		35 (94.6%)	22 (91.7%)	42 (95.5%)	
Chemotherapy regimen		.000				.000
CCLG-ALL-2008	38 (54.3%)		29 (78.4%)	3 (12.5%)	35 (79.5%)	
Modified BFM protocol	32 (45.7%)		8 (21.6%)	21 (87.5%)	9 (20.5%)	
Follow-up time, m		.060				.037
Median (range)	35.4 (1.2-90.2)		41.9 (9.3-90.2)	34.1 (6.4-88.3)	42.5 (9.3-90.2)	

IM/ND indicates insufficient metaphases/not done; IT, induction therapy.
* Haplo-HSCT cohort vs. nontransplant cohort.
† Nontransplant cohort vs. transplant cohort.

Survival analysis was performed using the Kaplan-Meier method with differences compared via the log-rank test. Multiple regression analysis for EFS, OS, and CIR was conducted using a multiple Cox regression model. Factors with $P < .1$ in the univariate analysis were adjusted in the multiple regression models. The chi-square test or Fisher exact test was used to analyze the differences in the distribution of individual parameters among patient subgroups. The CIR was estimated using competing risk analysis for nonrelapse mortality and relapse.

All statistical analyses were performed using SPSS software, version 19.0 (SPSS Inc., Chicago, IL) and R software packages (Bell Labs, New Providence, NJ). Statistical significance was defined as $P \leq .05$.

RESULTS

Patient Characteristics

From August 2010 to December 2016, 76 pediatric patients were newly diagnosed with Ph+ ALL. Of these, 6 patients were excluded for not receiving TKIs. The remaining 70 patients were assessable for this study, with a median age of 10 years (range, 1 to 17). The last follow-up was May 1, 2018, and the median follow-up period was 35.4 months (range, 1.2 to 90.2). The patient characteristics are summarized in Table 2.

Early Treatment Response and Affecting Factors

Sixty-three patients (90%) achieved CR after induction therapy, and 69 patients (98.6%) eventually achieved CR. Thirty-one patients (44.3%) achieved MMR after induction therapy, among which 16 achieved CMR. The initial WBC count was a risk factor for CR at the induction end ($P = .017$), whereas the other clinical features, molecular characteristics, and chemotherapy regimens, such as age, sex, positive myeloid antigen expression, *BCR-ABL* transcript, additional chromosome status, and *IKZF* deletion, did not influence the early treatment response (Table 3).

Outcomes

Figure 2 details the study flow. One patient abandoned treatment with no CR at the induction end and died on day 46; another patient died 6 days after completion of induction therapy due to a cerebrovascular accident, before beginning consolidation. The remaining 68 patients completed at least 2 consolidation cycles and then were nonrandomly divided into the nontransplant cohort and transplant cohort based on their preference. The patient characteristics of the 2 cohorts are listed in Table 2.

The transplant and nontransplant cohorts comprised 44 and 24 patients, respectively. The baseline characteristics were similar between the nontransplant and transplant cohorts. There was also no difference in the baseline characteristics between the haplo-HSCT and nontransplant cohorts, except for younger age in the nontransplant cohort ($P = .016$) (Table 2). However, the patients were much younger in the nontransplant cohort (median age, 10.5 years versus 8 years; $P = .027$), and the overall follow-up time was longer in the transplant cohort (42.5 versus 34.1 months; $P = .037$). In addition, whether in the transplant cohort or haplo-HSCT cohort, patients were mainly from the CCLG-ALL-2008 regimen ($P = .000$). Fifteen patients switched to dasatinib/ponatinib as a replacement for imatinib during the treatment—4 for CNSL, 10 for treatment failure (1 of whom with *T315I* mutation switched to ponatinib), and 1 for suspected CNSL due to repeated significant increase of cerebrospinal fluid protein.

Of the 44 patients in the transplant cohort, 3 had a 6/6 HLA-MSD, 37 had haplo-HSCT (2 with a 5/6 HLA-matched donor, 3 with a 4/6 HLA-matched donor, and 32 with a 3/6 HLA-matched donor), and the other 4 had a UCB donor (2 with a 6/6 HLA-matched donor, 1 with a 4/6 HLA-matched donor, and 1 with a 5/6 HLA-matched donor). The median time from diagnosis to transplant was 209.5 days (range, 110 to 477). All patients in the transplant cohort achieved myeloid engraftment at a median time of 12 days (range, 10 to 25), and all patients except 1 achieved platelet engraftment at a median time of 16 days (range, 10 to 87). The patient who did not achieve platelet engraftment died on day 65 after transplant. A total of 26 patients (1 UCB; 25 haplo) developed mild aGVHD (grades I to II). Five patients (haploidentical, n = 5) developed grades III to IV aGVHD. The 100-day cumulative incidence of

Table 3
Factors at Diagnosis Affecting Early Treatment Response

Factors	CR/All	Chi-square test	*P*	MMR/All	Chi-square test	*P*
Age, yr		.515	.473		.875	.471
<10	32/34			17/34		
≥10	31/36			14/36		
Sex		.852	.356		.012	.988
Male	43/46			20/46		
female	20/24			11/24		
WBC, $\times 10^9$/L		5.718	.017		1.568	.227
<100	43/44			22/44		
≥100	20/26			9/26		
CD13 and/or CD33		.917	.338		3.053	.097
Positive	28/33			11/33		
Negative	35/37			20/37		
Ph+ chromosome		1.022	.312		2.192	.169
T (9;22) only	32/34			16/34		
Other abnormalities	18/22			6/22		
BCR-ABL transcript		.000	1.000		2.402	.150
P190	49/55			27/55		
P210	14/15			4/15		
IKZF deletion		1.624	.203		.285	.594
Yes	12/15			8/15		
No	16/16			7/16		
Chemotherapy regimen		1.849	.174		.007	1.000
CCLG-ALL-2008	32/38			17/38		
Modified BFM protocol	31/32			14/32		

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

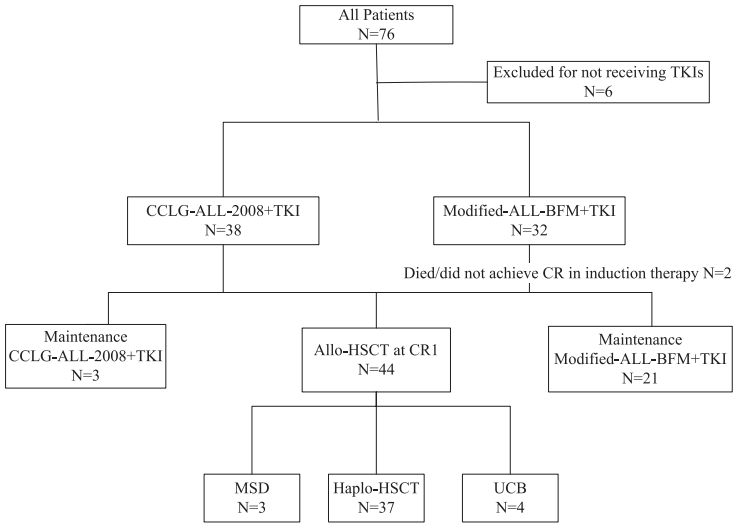

Figure 2. CONSORT diagram of all patients included in the study.

grades I to IV aGVHD was 65.8% ± 5.9% (95% confidence interval [CI], 48.6% to 81.0%), whereas that of grades III to IV aGVHD was 17.1% ± 7.1% (95% CI, 9.6% to 32.7%). Forty-two patients survived > 100 days post-transplant and were evaluated for chronic GVHD (cGVHD). Eighteen patients (haplo) developed cGVHD, which was limited in 8 cases and extensive in the remaining 10 patients. The 3-year cumulative incidences of overall chronic and extensive cGVHD were 46.1% ± 4.3% (95% CI, 32.2% to 54.7%) and 24.2% ± 6.5% (95% CI, 13.6% to 34.4%), respectively.

Relapse occurred in 16 patients (23.5%)—specifically, 7 (15.9%) in the transplant cohort (5 of whom underwent haplo-HSCT) and 9 (37.5%) in the non-transplant cohort—at a median time of 21.3 months (range, 13.3 to 33.5) in the transplant cohort and 7.1 months (range, 3.7 to 58.8) in the nontransplant cohort. Relapse included hematologic relapse (n = 14) and extramedullary leukemia relapse (n = 2). The 9 patients with relapse in the nontransplant cohort did not undergo allo-HSCT for further salvage treatment. By the end of the last follow-up, 15 patients had died at a median follow-up time of 25 months (range, 6.4 to 59.8). The causes of death included relapse (n = 13, 8 in the nontransplant cohort and 5 in the transplant cohort; haplo-HSCT = 4), and transplant-related complications (haploidentical, n = 2). Twenty patients underwent *BCR-ABL*

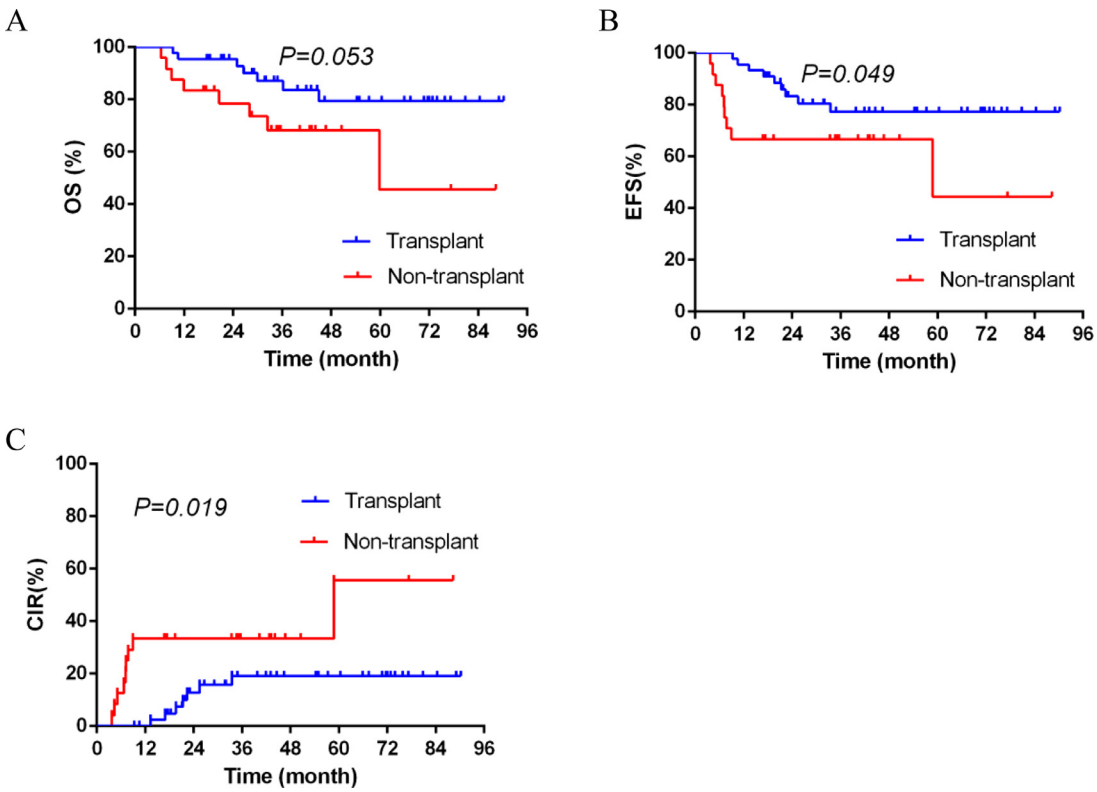

Figure 3. Kaplan-Meier estimates of 3-year outcomes in the transplant and nontransplant arms. (A) OS, (B) EFS, and (C) CIR.

point mutation detection, and 9 mutations were detected in 6 patients, including 2 patients with single *T315I*, 1 patient with *T315I* and *Y253H*, 1 patient with *T315I* and *E255K*, 1 patient with *T315I* and *F359V*, and 1 patient with single *Y253H*. All 6 children with *BCR-ABL* point mutations relapsed, and 5 had died by the last follow-up date.

The estimated 3-year probability of OS was 80.3% ± 5.2% (95% CI, 64.4% to 80.2%) in all 68 patients, 87.0% ± 5.5% in the transplant cohort, and 68.3% ± 10.1% in the nontransplant cohort (95% CI, 68.9% to 85.9% versus 43.4% to 75.2%; $P = .053$). The estimated 3-year probability of EFS was 73.4% ± 5.6% (95% CI, 60.1% to 77.1%) in all patients, 77.2% ± 6.8% in the transplant cohort, and 66.7% ± 9.6% in the nontransplant cohort (95% CI, 64.9% to 83.4% versus 37.2% to 71.6%; $P = .049$). The estimated 3-year probability of CIR was 23.5% ± 5.5% (95% CI, 14.8% to 37.2%) in the overall cohort, 14.9% ± 6.0% in the transplant cohort, and 40.6% ± 11.5% in the nontransplant cohort, respectively ($P = .019$; 95% CI, 6.8% to 33.0% versus 23.4% to 70.6%) (Figure 3). The estimated 3-year probabilities of OS, EFS, and CIR were 84.5% ± 6.4% (95% CI, 67.9% to 86.6%), 76.6% ± 7.3% (95% CI, 62.9% to 83.6%), and 14.8% ± 5.3% (95% CI, 7.3% to 29.9%) for the haplo-HSCT patients, respectively. The *P* values were .078, .076, and .026, respectively, when compared with that of the nontransplant cohort (Figure 4).

Factors Associated with Long-Term Survival and Relapse Rate

The results of the univariate analysis of factors associated with OS, EFS, and CIR in the overall cohort are shown in Table 4. Univariate analysis revealed that age, WBC count at presentation, and *BCR-ABL* levels after induction and at 3 months (whether MMR was achieved) were significant factors affecting OS, EFS, and CIR. Moreover, hematologic response after induction (whether CR was achieved) and treatment strategy (whether a transplant was received) were also significant factors that influenced EFS and CIR. In a multivariate model hematologic response after induction, *BCR-ABL* levels at 3 months, and transplant were independent prognostic factors associated with OS, EFS, and CIR, whereas age was a prognostic factor of OS and WBC count at presentation prognostic factor of CIR (Table 5).

For the 61 patients in the nontransplant and haplo-HSCT cohorts, the results of the univariate analysis of factors associated with OS, EFS, and CIR are shown in Table 6. Univariate analysis revealed that *BCR-ABL* levels after induction and at 3 months (whether to achieve MMR) were significant factors affecting OS, EFS, and CIR. Moreover, age was a significant factor that influenced OS and EFS, and WBC count at presentation and hematologic response after induction (whether CR was achieved) were significant factors that influenced EFS and CIR. In addition, platelets were also a significant factor affecting CIR. In a multivariate model hematologic response after induction, *BCR-ABL* levels at 3 months, and transplant were independent prognostic factors associated with OS, EFS, and CIR, whereas age was an independent factor of OS (Table 7).

Impact of Transplant Based on Prognostic Factors

We stratified the 68 patients in the transplant and nontransplant cohorts into 2 groups according to the 2 prognostic factors (hematologic response after induction and *BCR-ABL* levels at 3 months) that had independent significance on OS, EFS, and CIR based on the multivariate analysis in Table 5. The 2 groups were the standard-risk group (no poor prognostic factors, n = 40 [58.8%]) and the high-risk group (with ≥1 poor prognostic factors, n = 28 [41.2%]). In the standard-risk group (n = 40, transplant= 26, nontransplant = 14; median follow-up, 41.5 months; range, 9.3 to 89.1), there were no significant differences in the probabilities of 3-year OS (91.3% ± 5.9% versus 100%, $P = .297$), EFS (91.6% ± 5.7% versus 100%, $P = .303$), and

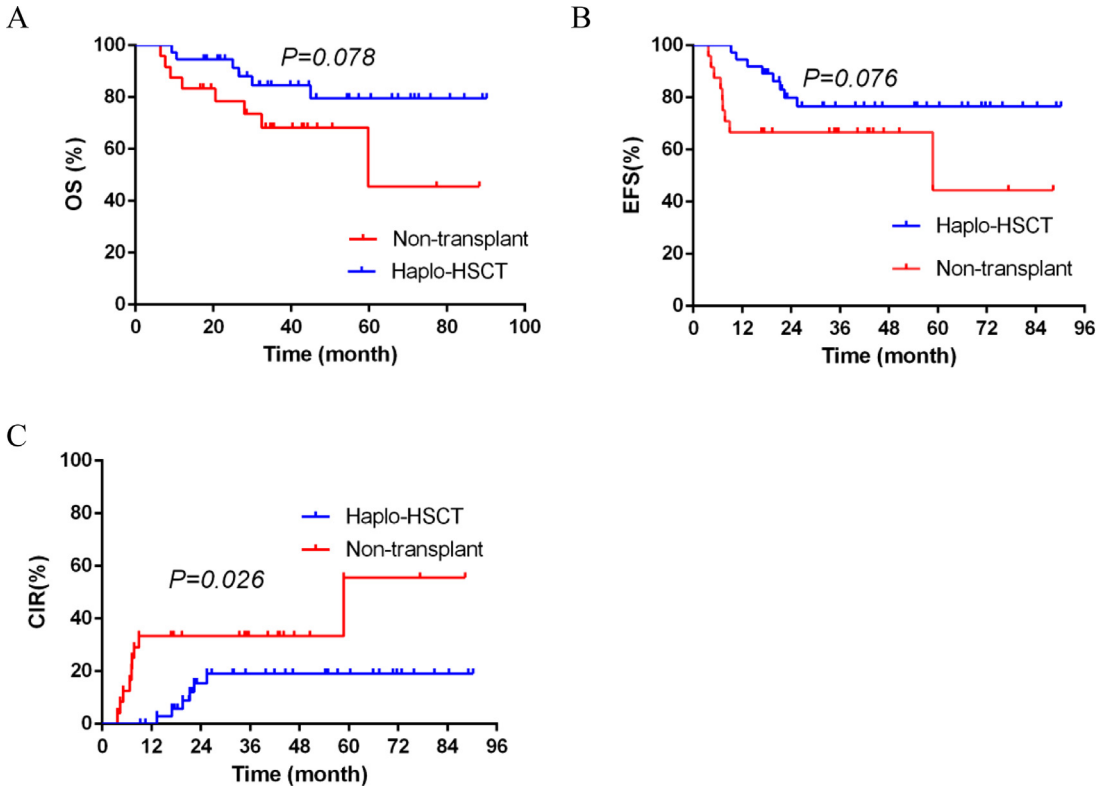

Figure 4. Kaplan-Meier estimates of 3-year outcomes in the haplo-HSCT and nontransplant arms. (A) OS, (B) EFS, and (C) CIR.

Table 4
Univariate Analysis of Factors at Diagnosis Associated with Long-Term Outcomes in Nontransplant and Transplant Cohorts (n = 68)

Factors	No. of Cases	3-Year OS(%)	*P*	3-Year EFS(%)	*P*	3-Year CIR(%)	*P*
Sex							
Male	46	80.9 ± 6.2	.668	76.7 ± 6.5	.605	22.2 ± 6.6	
Female	22	79.9 ± 9.1		66.6 ± 10.4		25.8 ± 10.1	.121
Age, yr							
<10	33	92.6 ± 5.2	.003	87.3 ± 6.0	.014	12.4 ± 6.1	
≥10 (n = 35)	35	69.6 ± 8.1		60.9 ± 8.6		33.2 ± 8.2	.047
WBC, $\times 10^9$/L							
<100	43	88.1 ± 5.0	.048	87.7 ± 5.2	.004	9.3 ± 4.3	
≥100	26	69.7 ± 9.7		51.3 ± 10.3		44.3 ± 10.2	.002
Hemoglobin, g/L							
≤101	35	84.5 ± 6.4	.294	72.7 ± 7.8	.881	25.5 ± 8.1	
>101	33	75.6 ± 8.1		74.8 ± 7.8		21.2 ± 6.8	.664
Platelet count, $\times 10^9$/L							
≥55	33	83.1 ± 6.9	.426	76.0 ± 8.1	.269	14.7 ± 6.5	
<55	35	78.0 ± 7.5		70.9 ± 7.8		32.2 ± 8.6	.087
CD13 and/or CD33							
Positive	32	80.5 ± 7.2	.733	74.6 ± 7.8	.868	24.2 ± 7.6	
Negative	36	79.7 ± 7.6		72.0 ± 8.1		22.7 ± 7.4	.881
Ph+ chromosome							
T (9;22) only	33	79.9 ± 7.4	.190	79.9 ± 7.4	.075	18.1 ± 7.9	
Other abnormalities	21	72.4 ± 10.9		59.3 ± 11.3		30.7 ± 8.9	.266
BCR-ABL transcript							
P190	54	81.5 ± 5.7	.785	72.1 ± 6.4	.588	24.2 ± 6.3	
P210	14	78.6 ± 11.0		77.1 ± 11.7		20.6 ± 10.9	.769
IKZF deletion							
Yes	14	88.9 ± 10.5	.668	73.1 ± 13.6	.979	23.2 ± 11.1	
No	16	81.3 ± 9.8		79.5 ± 10.7		15.1 ± 8.7	.593
CR after IT							
Yes	62	82.0 ± 5.2	.076	79.6 ± 5.3	.000	17.6 ± 5.2	
No	6	62.5 ± 21.3		16.7 ± 15.2		73.1 ± 13.6	.000
MMR after IT							
Yes	31	92.9 ± 4.9	.004	91.7 ± 5.6	.001	6.5 ± 4.7	
No	37	71.2 ± 7.8		56.8 ± 8.6		38.0 ± 8.4	.008
MMR after 3 mo							
Yes	44	87.2 ± 5.4	.001	86.8 ± 6.6	.000	9.2 ± 4.9	
No	24	60.2 ± 10.5		48.8 ± 10.5		49.6 ± 10.9	.000
Chemotherapy regimen							
CCLG-ALL-2008	38	83.4 ± 6.2	.631	72.1 ± 7.6	.751	23.7 ± 7.4	
Modified BFM protocol	30	76.5 ± 7.8		75.6 ± 8.8		23.5 ± 7.8	.454
Transplant							
Yes	44	87.0 ± 5.5	.053	77.2 ± 6.8	.049	14.9 ± 6.0	
No	24	68.3 ± 10.1		66.7 ± 9.6		40.6 ± 11.5	.019

CIR (4.7% ± 4.6% versus 0%, *P* = .469) between the transplant and nontransplant cohorts. In the high-risk group (n = 28, transplant = 18, nontransplant = 10; median follow-up, 32.1 months; range, 6.4 to 90.2), the 3-year OS (81.4% ± 9.8% versus 26.7% ± 15.0%, *P* = .004), EFS (58.4% ± 12.3% versus 20.0% ± 12.6%, *P* = .000), and CIR (38.1% ± 12.5% versus 89.0% ± 9.5%, *P* = .000) were significantly better in the transplant cohort than that in the nontransplant cohort. In addition, we further compared the survival of children in the standard-risk (n = 26) and high-risk (n = 14) groups in the transplant cohort. The 3-year OS (91.3% ± 5.9% versus 81.4% ± 9.8%, *P* = .098), EFS (91.6% ± 5.7% versus 58.4% ± 12.3%, *P* = .017), and CIR (4.7% ± 4.6% versus 38.1% ± 12.5%, *P* = .010) were better in the standard-risk than that in the high-risk group.

Similarly, we stratified the 61 patients in the haplo-HSCT and nontransplant cohorts into 2 groups according to the same 2 prognostic factors (described above) based on the multivariate analysis in Table 7. In the standard-risk group (n = 37, transplant = 23, nontransplant = 14; median follow-up, 40.3 months; range, 9.3 to 89.1), there was no significant difference in probabilities of 3-year OS (90.0% ± 6.8% versus 100%, *P* = .262), EFS (90.3% ± 6.5% versus 100%, *P* = .269), and CIR

Table 5
Multivariate Analysis of Prognostic Factors Associated with Long-Term Outcomes in Nontransplant and Transplant Cohorts (n = 68)

Variable	OS HR (95% CI)	*P*	EFS HR (95% CI)	*P*	CIR HR (95% CI)	*P*
Age ≥ 10 yr	6.699 (1.400-32.050)	.017	2.933 (.817-10.532)	.099	2.331 (.535-10.152)	.260
WBC ≥ 100 × 10^9/L	1.925 (.558-6.636)	.300	3.460 (.775-15.448)	.104	5.017 (1.266-19.888)	.022
CR after IT	4.678 (1.075-20.362)	.040	22.609 (4.637-110.236)	.000	12.754 (3.096-52.544)	.000
MMR after IT	2.767 (.423-18.110)	.288	2.974 (.515-17.178)	.223	3.700 (.609-22.463)	.155
MMR after 3 mo	4.260 (1.268-14.313)	.019	8.414 (2.178-32.501)	.002	11.204 (3.258-38.536)	.000
Transplant	5.171 (1.589-16.831)	.006	4.926 (1.544-15.717)	.007	10.647 (2.834-40.000)	.000
Ph+ chromosome T (9;22) only			1.313 (.378-4.567)	.668		
Platelets ≥ 55 × 10^9/L					1.359 (.341-5.418)	.664

HR indicates hazard ratio.

Table 6
Univariate Analysis of Factors at Diagnosis Associated with Long-Term Outcomes in Nontransplant and Haplo-HSCT Cohorts (n = 61)

Factors	No. of Cases	3-Year OS(%)	*P*	3-Year EFS(%)	*P*	3-Year CIR(%)	*P*
Sex							
Male	41	78.6 ± 6.8	.993	73.8 ± 7.2	.902	24.3 ± 6.7	
Female	20	77.6 ± 10		69.3 ± 10.5		23.4 ± 9.8	.938
Age, yr							
<10	29	91.5 ± 5.9	.009	85.4 ± 6.8	.032	14.0 ± 6.8	
≥10	32	66.7 ± 8.7		61.6 ± 8.8		32.4 ± 8.0	.095
WBC, $\times 10^9$/L							
<100	36	85.6 ± 6.0	.166	86.1 ± 5.8	.023	10.7 ± 5.4	
≥100	25	68.2 ± 10.1		54.6 ± 10.2		41.4 ± 10.1	.007
Hemoglobin, g/L							
≤101	32	83.0 ± 7.0	.150	74.0 ± 8.0	.642	24.6 ± 7.8	
>101	29	72.3 ± 9.1		71.4 ± 8.6		23.3 ± 6.7	.903
Platelet count, $\times 10^9$/L							
≥55	29	80.9 ± 7.8	.288	77.5 ± 8.2	.176	12.9 ± 6.0	
<55	32	75.8 ± 8.1		68.1 ± 8.4		34.5 ± 8.9	.049
CD13 and/or CD33							
Positive	30	79.1 ± 7.6	.610	72.9 ± 8.2	.822	25.2 ± 7.5	
Negative	31	76.3 ± 8.6		71.8 ± 8.6		22.7 ± 8.1	.810
Ph+ chromosome							
T (9;22) only		77.1 ± 8.3	.314	77.1 ± 8.3	.146	20.7 ± 8.9	
Other abnormalities		72.4 ± 10.9		59.3 ± 11.3		30.6 ± 9.4	.408
BCR-ABL transcript							
P190	47	78.7 ± 6.4	.682	70.7 ± 6.9	.480	25.3 ± 6.1	
P210	14	78.6 ± 11.0		77.1 ± 11.7		19.8 ± 11.7	.660
IKZF deletion							
Yes	14	88.9 ± 10.5	.507	73.1 ± 13.6	.767	23.2 ± 11.7	
No	13	74.0 ± 13.2		74.0 ± 13.2		19.0 ± 11.1	.801
CR after IT							
Yes	55	79.6 ± 5.8	.100	79.6 ± 5.5	.001	17.6 ± 5.3	
No	6	62.5 ± 21.3		16.7 ± 15.2		69.9 ± 11.8	.000
MMR after IT							
Yes	28	92.0 ± 5.4	.006	90.9 ± 6.1	.001	7.0 ± 4.5	
No	33	67.8 ± 8.5		56.1 ± 8.9		38.6 ± 9.7	.010
MMR after 3 mo							
Yes	41	91.3 ± 4.9	.000	86.1 ± 5.8	.000	11.6 ± 6.6	
No	20	52.6 ± 11.7		45 ± 11.1		50.8 ± 11.4	.000
Chemotherapy regimen							
CCLG-ALL-2008	32	80.2 ± 7.3	.736	70.7 ± 8.3	.854	24.3 ± 8.1	
Modified BFM protocol	29	75.7 ± 8.0		75.3 ± 8.9		24.3 ± 8.0	.515
Transplant							
Yes	37	84.5 ± 6.4	.078	76.6 ± 7.3	.076	14.8 ± 5.3	
No	24	68.3 ± 10.1		66.7 ± 9.6		39.6 ± 10.9	.026

(5.5% ± 5.4% versus 0%, *P* = .434) between the transplant and nontransplant cohorts. In the high-risk group (n = 24, transplant = 14, nontransplant = 10; median follow-up, 30.9 months; range, 6.4 to 90.2), the 3-year OS (76.6% ± 11.9% versus 26.7% ± 15.0%, *P* = .015), EFS (56.3% ± 13.5% versus 20.0% ± 12.6%, *P* = .002), and CIR (39.3% ± 13.8% versus 89.0% ± 9.5%, *P* = .001) were also significantly better in the transplant cohort than that in the nontransplant cohort. We further compared the survival of children in the standard-risk (n = 23) and high-risk (n = 14) groups in the haplo-HSCT cohort. The 3-year OS (90.0% ± 6.8% versus 76.6% ± 11.9%, *P* = .143), EFS (90.3% ± 6.5% versus 56.3% ± 13.5%, *P* = .020), and CIR (5.5% ± 5.4% versus 39.3% ± 13.8%, *P* = .013) were better in the standard-risk than that in the high-risk group.

DISCUSSION

Treatment outcomes for children with Ph+ ALL have substantially improved in recent years due to the introduction of TKIs and improvements in chemotherapy and HSCT methods. In this study the 3-year OS and EFS of the 68 patients enrolled were 80.3% ± 5.2% and 73.4% ± 5.6%, respectively. The OS rate in our center is excellent, which is probably due to the intensive use of

Table 7
Multivariate Analysis of Prognostic Factors Associated with Long-Term Outcomes in Nontransplant and Haplo-HSCT Cohorts (n = 61)

Variable	OS HR (95% CI)	*P*	EFS HR (95% CI)	*P*	CIR HR (95% CI)	*P*
Age ≥ 10 yr	5.830 (1.171-29.039)	.031	2.734 (.751-9.952)	.127	1.852 (.413-8.296)	.420
WBC ≥ 100 × 10^9/L			2.626 (.742-9.297)	.134	3.965 (.958-16.415)	.057
CR after IT	4.797 (1.037-22.177)	.045	11.319 (3.158-40.563)	.000	13.286 (2.949-59.860)	.001
MMR after IT	2.618 (.398-17.216)	.317	4.462 (.788-25.266)	.091	3.327 (.563-19.654)	.185
MMR after 3 mo	3.882 (1.126-13.389)	.032	8.143 (2.795-23.718)	.000	10.004 (2.913-34.362)	.000
Transplant	5.345 (1.468-19.458)	.011	4.053 (1.427-14.204)	.010	10.780 (2.520-46.107)	.001
Platelets ≥ 55 × 10^9/L					1.799 (.402-8.046)	.442

TKI and high proportion of transplants. Moreover, the result is comparable with that reported by other centers [4, 6, 7].

The initial WBC count has always been considered as an important factor affecting the prognosis of Ph+ ALL [2, 10, 11, 14, 21]. In this study we also found that an high initial WBC count ($\geq 100 \times 10^9$/L) was a risk factor affecting early treatment response and 3-year CIR. Although CR was eventually achieved in 69 of 70 children (98.6%) who completed at least induction therapy in this study, the CR and MMR rates after induction were only 90% and 44.3%, respectively, which is lower than that reported by the Spanish Cooperative Group SHOP [7] and St. Jude Children's Research Hospital [22]. This difference may be related to the high proportion of high WBC count at presentation ($\geq 100 \times 10^9$/L, 26/70 [37.1%]) and administration of different types of TKIs.

In Ph+ ALL, MRD at the early phase of treatment was a significant prognostic factor for long-term remission and survival in several studies [23-26]. Similarly, several adult trials in the current TKI era reported that the achievement of deeper levels of MRD assessed via quantitative PCR for the *BCR-ABL* transcript is also important in patients with Ph+ ALL according to a number of studies [14, 21, 27, 28]. In a prospective study by Ravandi et al. [21], PCR assessment of MRD in 76 of 122 Ph+ ALL patients who did not undergo HSCT showed that patients achieving MMR at 3, 6, 9, and 12 months had better long-term OS. In another study by Lee et al. [27], of 95 patients treated with imatinib-based chemotherapy followed by subsequent allogeneic HSCT, the early stable molecular responders (patients showing early and persistent MMR or CMR by the end of 2 courses of chemotherapy) had better disease-free survival and lower relapse. Short et al. [28] reported that patients with Ph+ ALL who achieve CMR at 3 months have superior survival to those with lesser molecular responses and have excellent long-term outcomes even without HSCT. Recently, Cazzaniga et al. [29] also reported that early MRD negativity is highly predictive of favorable outcomes for childhood Ph+ ALL. According to their study the earlier MRD negativity is achieved, the better the prognosis. In the present study we found a significant correlation between early deep molecular response and long-term outcome. According to Lee et al. [27], different regimens and clinical factors could account for the discrepancy between the results. Patients in our study received induction treatment with a CODPL regimen (modified ALL-BFM, n = 30) or VDLD (vincristine + daunomycin/idarubicin + pegaspargase + dexamethasone/prednisone) regimen (CCLG-ALL-2008, n = 38) combined with first-generation TKIs; the early treatment response and MMR rate at 3 months between the 2 regimens were comparable.

Even in the present TKI era, HSCT still plays an important role in the treatment of pediatric patients with Ph+ ALL. According to the results of EsPhALL [4] conducted in parallel to Children's Oncology Group AALL003 [5], patients who underwent HSCT showed statistically superior outcomes to the non-transplant cohort; however, these studies are limited by the small number of patients who did not receive allo-HSCT. In another key study (SHOP/ALL-2005), the 5-year EFS of patients who received continuous intermediate-dose imatinib (260 mg/m^2) from day 15 of induction in combination with intensive chemotherapy, followed by HSCT from a matched related or unrelated donor, is significantly higher than that of the preimatinib cohort (81.3% versus 29.6%); however, the number of patients was small (n = 16) [30]. In the present study multivariate analysis showed a significant advantage of HSCT on survival. However, not all children with Ph+ ALL require HSCT. A study by Jeha et al. [22] showed that in the current TKI era, high survival rates can be obtained without HSCT in children with Ph+ ALL who achieve negative MRD status at the end of remission induction therapy when implementing MRD-directed stratified treatment. In this study we found that children in the standard-risk group remained in long-term remission even without undergoing transplant, whereas HSCT conferred significant survival advantages for patients in the high-risk group. Our results confirm the necessity of risk-stratification management in the treatment of children with Ph+ALL.

A haploidentical-related donor is 1 of the most important alternative sources for those without MSD or a matched unrelated donor. In our previous study we found that patients who underwent haplo-HSCT achieved outcomes similar with those of matched related transplants during the same period and matched sibling transplants reported by another center for adult patients with Ph+ ALL [16]. In a pediatric study from our center by Chen et al. [12], haplo-HSCT could also achieve promising long-term survival for pediatric patients with Ph+ ALL. In this study we also found that durable remissions and long-term survival can be achieved with the combination of chemotherapy and TKIs followed by haplo-HSCT in pediatric patients with Ph+ ALL, as the estimated 3-year probabilities of OS, EFS, and CIR for the 37 patients with haplo-HSCT were 84.5% ± 6.4%, 76.6% ± 7.3%, and 14.8% ± 5.3%, respectively. Moreover, when further risk-stratification analysis was performed, haplo-HSCT showed significant superiority in the high-risk group, which demonstrated the excellent efficacy and safety of haplo-HSCT in the risk stratification–tailored treatment for children with Ph+ ALL.

Despite our findings of favorable outcomes of allo-HSCT and haplo-HSCT in the high-risk group, this study had some limitations. First, this is not a randomized controlled trial, as the choice of treatment was determined by the guardian's wishes. Second, although the patients were initially randomly assigned to 2 different regimens, there may be differences in the composition and dosage of some chemotherapy drugs between the 2 regimens. However, there were no significant differences in the early treatment response and MMR rate at 3 months between the 2 regimens, and most patients in the CCLG-2008 cohort chose to undergo transplant eventually. Thus, the long-term effectiveness of chemotherapeutic agents mainly depended on the modified ALL-BFM cohort. Third, this study is a single-center study with a small sample size, particularly the chemotherapy + TKI group.

In summary, our data indicate that hematologic response after induction and *BCR-ABL* levels at 3 months are likely to be useful in identifying subgroups of pediatric Ph+ ALL at high risk of relapse. Children with Ph+ ALL may benefit from allo-HSCT in first CR, particularly patients in the high-risk group. Haplo-HSCT could achieve promising long-term survival for pediatric Ph+ ALL. Thus, haplo-HSCT can be an alternative approach for Ph+ ALL patients in the high-risk group. Our results should be validated in further systematic studies with large numbers of pediatric Ph+ ALL patients.

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the manuscript and were responsible for the critical review and revision of this manuscript. L.P.Z. and X.J.H. were the principal investigators, designed the research, interpreted the data, and wrote the manuscript. All authors provided the approval of the final manuscript for submission.

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