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RESEARCH

Allogeneic stem cell transplantation is still a highly curative therapy in adults with philadelphia chromosome–positive acute lymphoblastic leukaemia

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Abstract

The application of tyrosine kinase inhibitors (TKIs) and novel immunotherapies has improved outcomes in patients with Ph+acute lymphoblastic leukaemia (ALL), and the issue of whether there is still a need for stem cell transplantation has become controversial. We performed a retrospective study to explore whether stem cell transplantation still held a place in patients with Ph+ALL if only imatinib and 2nd generation TKIs are available and affordable. A total of 292 patients were included. The median age was 38 years [range 14–64, IQR 28–48]. Patients receiving transplants ($n=216$) had better rates of 4-year disease-free survival (DFS, 68% vs. 24%, $P<.0001$) and overall survival (OS, 72% vs. 47%, $P<.0001$) than those receiving continuous TKIs plus chemotherapy (TKI-chemo) ($n=76$). In the multivariate analysis, male sex, WBC count $\geq 95\times10^9$/L and PLT count $\leq 154\times10^9$/L at diagnosis were significantly associated with poorer outcomes, and transplantation was significantly associated with favourable DFS and OS. In addition, the transplant outcomes were superior in any subgroup according to the number of risk variables. Furthermore, propensity score matching (PSM) analyses showed similar findings in the whole cohort and in age- and *BCR-ABL1* level-based subgroups after the first or second consolidation. In conclusion, transplantation as a one-time procedure for adults with Ph+ALL patients remains important in countries lacking accessibility to third-generation TKIs or immunotherapies, regardless of the depth of the molecular response.

Keywords Philadelphia chromosome–positive acute lymphoblastic leukaemia · Tyrosine kinase inhibitors · Molecular response · Allogeneic stem cell transplantation

Introduction

Philadelphia chromosome–positive (Ph+) acute lymphoblastic leukaemia (ALL) accounts for approximately 20–30% of ALL cases in adults [1–3]. Before the introduction of tyrosine kinase inhibitors (TKIs), the complete remission rate (CR) was 46–90%, and the 3-year overall survival (OS) rate was less than 10% with intensive chemotherapy and 30–40% if the patient underwent allogeneic stem cell transplantation (allo-HSCT) at the first CR; therefore, induction with intensive chemotherapy followed by allo-HSCT has become the standard therapy [4–7].

The advent of TKIs has led to a major therapeutic advancement in patients with Ph+ALL over the past 20 years, not only in combination with chemotherapy but also in combination with allo-HSCT. With the application of imatinib or dasatinib plus chemotherapy, the CR rates were reported as 90–96%, and

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the 3-5-year OS rates were reported as 30–50% [8–11]. With advances in transplantation techniques and TKI combinations, the outcomes have obviously improved in recent decades when treating Ph+ALL, with a disease-free survival (DFS) rate of 81% [12], and haploidentical transplantation (haplo-HSCT) was found to exhibit a stronger graft versus leukaemia (GVL) effect than human leukocyte antigen (HLA)-matched donor transplantation [13, 14]. The emergence of third-generation TKIs and new immune therapies, including blinatumomab, has further improved outcomes, resulting in CR rates close to 100% and 3-year OS rates greater than 70% [7, 15, 16]. Several studies have shown that early achievement of complete molecular remission (CMR) in Ph+ALL is an important indicator predicting prolonged survival and no need for allo-HSCT [15, 17–19]. Thus, the question that has been asked among researchers for a decade: is transplantation clinically imperative in patients with Ph+ALL in the era of TKIs±immunotherapy? In certain developing countries, third-generation TKIs and immunotherapies are not widely available and are more expensive than transplantation. Therefore, we performed a retrospective study to explore whether transplantation still holds a place in patients with Ph+ALL from countries lacking accessibility to third-generation TKIs or immunotherapies.

Methods

Patients

From January 2009 to July 2022, data from consecutive patients newly diagnosed with Ph+ALL who were treated at Peking University People's Hospital and achieved CR were reviewed. Patients included in this study were assigned to the combination of TKIs and chemotherapy (TKI-chemo) group or the transplantation group (after at least one cycle of consolidation therapy) based on their own preferences. Patients were followed until the end of the study evaluation period on October 1, 2022. All patients signed informed consent forms before beginning treatment. The study protocol was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Peking University People's Hospital.

Diagnosis and cytogenetic/molecular analysis

The diagnosis of ALL was confirmed by morphology and/or immunophenotyping [20]. Cytogenetic analysis was performed by the G-banding technique. *BCR-ABL1* transcripts were detected by real-time quantitative polymerase chain reaction (PCR). Bone marrow samples were used for analysis. The normalization ratio of the *BCR-ABL1* transcript level was obtained through comparison with the ABL transcript level, as reported previously [21]. There were at least 32,000 ABL transcript copies. Ikaros family zinc finger protein 1 (IKZF1) was detected using multiplex fluorescent PCR [22]. IKZF1 deletion was reviewed and detected in the available patient samples.

Tyrosine kinase inhibitors

Imatinib or dasatinib was administered from the beginning of induction therapy until relapse, death or transplantation. Since 2014, when dasatinib was available in China, patients with no severe pleuro-pulmonary or pericardial diseases received dasatinib; moreover, patients receiving initial imatinib switched to dasatinib when treatment failure occurred if had no dasatinib-resistant *BCR-ABL1* mutations, including T315I, V299L, T315A, and F317L/V/I/C. The initial doses of imatinib and dasatinib were 400 mg and 100 mg daily, respectively, and were adjusted according to the emergence of TKI-related toxicities during induction, consolidation and maintenance treatment. In this study, at the beginning of induction therapy, no patients received third-generation TKIs (such as ponatinib or olverembatinib), but 4 patients received ponatinib when they relapsed after transplantation. The maintenance treatment of TKI lasted for approximate two years.

Chemotherapy

The CODP or VP regimen was used as the induction treatment as previously described [11]. The CODP regimen was used before 2013; the VP regimen has since been used due to better safety and equal effectiveness. A modified hyper-CVAD regimen [23] was used as the consolidation treatment, including intrathecal methotrexate and/or cytosine arabinoside administration and central nervous system leukaemia (CNSL) prevention.

Transplantation

The detailed HSCT protocols, including donor selection, HLA typing, and stem cell harvesting, have been described in previous studies [24, 25]. Preventive TKIs were administered as prophylaxis strategy, then switched once *BCR-ABL1* turned positive post HSCT [26].

Third-generation TKIs were not involved in the post-HSCT relapse prophylaxis strategy in this study, and no patients received blinatumomab or inotuzumab. Four patients received chimeric antigen receptor T-cell (CAR-T) therapy when they relapsed after transplantation.

Definitions

CR was defined as no circulating blasts or extramedullary disease, normal bone marrow cellularity with < 5% blasts, together

with an absolute neutrophil count > 1.5×10^9/L and platelet (PLT) count > 100×10^9/L, and no relapse for 4 weeks. Early death was defined as death before treatment response could be assessed. Relapse was defined by the reappearance of blasts in peripheral blood, ≥ 5% blasts in bone marrow, or extramedullary leukaemia in patients with previously documented CR. CMR was defined as *BCR-ABL1* transcripts < 0.01% via polymerase chain reaction (PCR) assay, and it was defined as 0% when the level of *BCR-ABL1* transcripts was not detected [27]. ABL1 mutation was detected by the direct sequencing method following treatment failure once 1 of the following events occurred: (1) failure to obtain CR after a 4-week induction, (2) > 1 log increase in *BCR-ABL1* level during therapy, (3) recurrence of *BCR-ABL1* transcripts after achieving a CMR, or (4) haematologic relapse [11]. DFS was calculated from the date of CR to relapse or death or censored at last follow-up. OS was calculated from the date of diagnosis to death due to any cause or censored at last follow-up.

Statistical analysis

Descriptive statistics were used to summarize covariates. Categorical covariates are reported as percentages and counts. Continuous variables are reported as medians and ranges or interquartile ranges (IQRs). Pearson's chi-square test was used to analyse categorical covariates. Student's t (normal distribution) or Mann–Whitney U (nonnormal distribution) tests were used to compare continuous covariates between groups. DFS and OS were calculated by the Kaplan–Meier method and compared by the log-rank test. Cox regression models were used for univariate and multivariate analyses to identify covariates associated with DFS and OS. The variance inflation factor (VIF) was estimated to check for multicollinearity among covariates included in the Cox model [28]. Covariates with $P < .2$ in the univariable analyses were included in the multivariable analyses. Propensity score matching (PSM) was performed to adjust for differences in baseline covariates between subjects receiving or not receiving allo-HSCT and balance evaluated using a calliper width of 0.2 [29]. A 2-sided $p < .05$ was considered significant. SPSS 22.0 (SPSS, Chicago, IL), R version 4.2.2 (R Core Team, Vienna, Austria) and GraphPad Prism 8 (GraphPad Software Inc., La Jolla, CA) were used for analysis and graphing.

Results

Patients

From January 2009 to July 2022, data from 299 consecutive patients with Ph + ALL were reviewed. Five patients (2%) who suffered from early death and 2 who had no remission were excluded, leaving 292 (98%) patients who achieved CR to be included in this study. A total of 161 patients (55%) were male. The median age was 38 years [range 14–64]. A total of 205 patients (70%) had the *BCR-ABL1* p190 subtype; 87 (30%) had the *BCR-ABL1* p210 subtype. A total of 142 patients (62%) out of 229 with available samples were identified as harbouring the IKZF1 deletion. Among the 292 patients, 148 patients (51%) received initial imatinib; 144 (49%) received dasatinib. The patients' characteristics are summarized in Table 1. At the timepoints of CR, the first consolidation and the second consolidation, a total of 292, 282, and 197 patients were evaluable for *BCR-ABL1*, and the proportions of patients achieving CMR were 15%, 38%, and 42%, respectively.

Seventy-one patients experienced treatment failure in the TKI-chemo group and transplantation group before transplantation, and 56 ABL mutations were detected in 40 patients, including T315I, E255K, G250E, E459K, and E255V, followed by E255K, F317L, K247R, M441L, E255K/V, E355G, F359V, F317I, F486S, Y253H and R386-L387insW.

A total of 216 patients (74%) underwent HSCT in CR1 (transplantation group) after completing at least 1 consolidation cycle (184 cases after the first consolidation and 32 cases after the second consolidation), including 65 transplants from matched sibling donors, 145 from haploidentical donors and 6 from unrelated donors. Seventy-six (26%) patients received continuous TKIs and chemotherapy (TKI-chemo group) by their own choice, as shown in Table 1. The transplant group was younger (median age: 35 vs. 48 years, $P < .001$) with a lower bone marrow (BM) blast percentage at diagnosis (88% vs. 91%, $P = .019$).

In the TKI-chemo group, with a median follow-up period of 12 months (IQR, 7 to 24) for all 76 patients and 14 months (IQR, 6 to 28) for the 49 surviving patients, 16 patients relapsed at a median of 5 months (IQR, 2 to 16), and 27 died of relapse at a median follow-up of 4 months (IQR, 3 to 8). The 2-year DFS and OS rates were 31% (95% CI 18%, 45%) and 58% (95% CI 45%, 72%), respectively.

In the transplantation group, all patients achieved myeloid engraftment. With a median follow-up period of 40 months for all 216 patients and 45 months (IQR, 20 to 79) in 170 surviving patients, 21 patients relapsed at a median of 40 months (IQR, 16 to 75), and 45 died of relapse ($n = 44$) or transplant-related mortality ($n = 1$) at a median follow-up of 14 months (IQR, 10 to 27). The 6-year DFS and OS rates were 61% and 73%, respectively (Fig. 1A-B). The transplantation group had longer median DFS (44 versus 12 months, $P < .0001$) and OS (50 versus 19 months, $P < .0001$) than the TKI-chemo group.

Identification of prognostic factors

In the 292 CR patients, characteristics at diagnosis (including gender, age, white blood cell (WBC) count, haemoglobin

Table 1 Patients characteristics

	[ALL]	TKI-chemo	Transplantation	*P* value
	N = 292	*N* = 76	*N* = 216	
Gender, n (%):				0.669
Male	161 (55%)	44 (58%)	117 (55%)	
Female	131 (45%)	32 (42%)	99 (46%)	
Age, year median (range)	38 [14; 64]	48 [21; 63]	35 [14; 64]	< 0.001
WBC, $\times 10^9$/L median (range)	40 [1; 488]	52 [2; 443]	38 [1; 488]	0.284
Hemoglobin, g/L median (range)	103 [11; 187]	106 [35; 165]	103 [11; 187]	0.813
Platelet, $\times 10^9$/L median (range)	46 [1; 403]	40 [4; 310]	48 [1; 403]	0.302
Blasts in BM, % median (range)	89 [21; 99]	91 [22; 99]	88 [21; 98]	0.019
Chromosome:				0.543
standard t (9; 22)	81 (29%)	25 (34%)	56 (27%)	
Normal	47 (17%)	9 (12%)	38 (19%)	
Additional chromosomal aberration	137 (49%)	37 (50%)	100 (49%)	
No split phase	14 (5%)	3 (4%)	11 (5%)	
BCR-ABL transcript type, n (%):				1.000
P190	205 (70%)	53 (70%)	152 (70%)	
P210	87 (30%)	23 (30%)	64 (30%)	
Initial TKI used, n (%):				0.180
Imatinib	148 (51%)	33 (43%)	115 (53%)	
Dasatinib	144 (49%)	43 (57%)	101 (47%)	

Abbreviations: white blood cell (WBC), blasts in bone marrow (BM), Hemoglobin, Platelets, tyrosine kinase inhibitor (TKI)

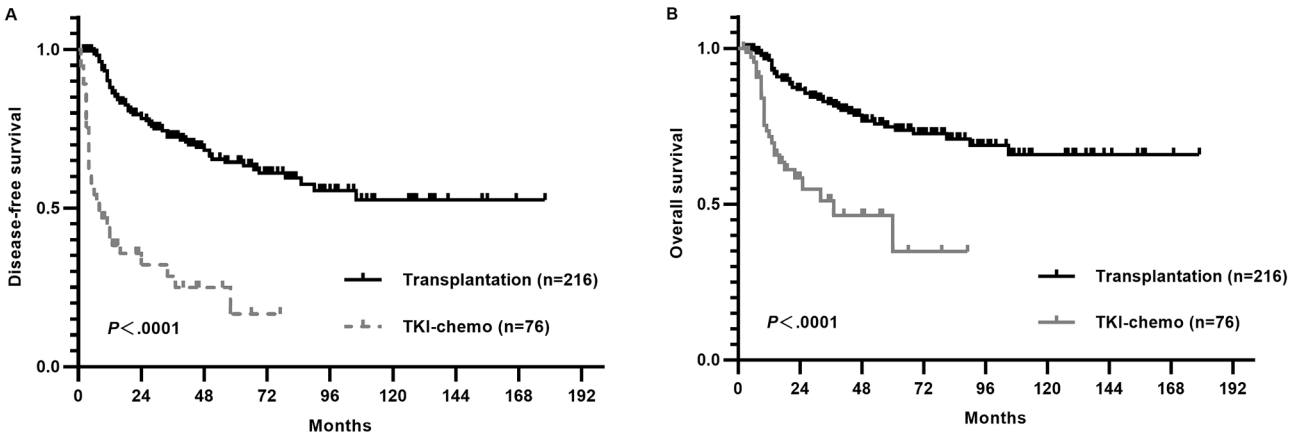

Fig. 1 Outcomes in the transplantation and TKI-chemo groups among the entire population

concentration, platelet count, blasts in BM, chromosome karyotype, *BCR-ABL1* transcript type, and IKZF1 deletion status), initial TKI and induction chemotherapy used, haematologic response after the 4-week induction, *BCR-ABL1* levels after induction and at the first consolidation cycle, and whether or not transplantation was performed were analysed to identify factors associated with outcomes. The univariate analysis results are shown in Supplementary Table 1. In the multivariate analysis, both male sex and not undergoing transplantation were significantly associated with poor DFS and OS, while a PLT count $\leq 154 \times 10^9$/L and a WBC count $\geq 95 \times 10^9$/L were associated with poor DFS (Table 2). However, *BCR-ABL1* levels at the time of achieving CR and after the first consolidation chemotherapy were not associated with DFS and OS (Supplementary Table 1).

To assess the role of transplantation, the patients were divided into 3 groups according to the 3 risk factors (male, WBC counts $\geq 95 \times 10^9$/L and PLT counts $\leq 154 \times 10^9$/L at diagnosis): the low-risk subgroup (with no or one factor, $n = 117$, 40%), intermediate-risk subgroup (2 factors, $n = 136$, 47%), and high-risk subgroup (3 factors, $n = 39$, 13%). The outcomes of transplantation were superior to those of TKI-chemo in any subgroup (Fig. 2A-F).

To further identify prognostic factors, we conducted a multivariate analysis in 197 patients who completed the second consolidation cycle and found that male sex, WBC

Table 2 Multivariate analysis of outcomes of the whole cohort ($n=292$) and patients who completed the second consolidation cycle ($n=197$)

Outcome	Hazard ratio (95%Confidence interval)	*P* value
the whole cohort ($n=292$)		
Disease free survival		
Male	1.927 (1.288–2.881)	0.002
WBC ≥ 95*10^9/L	1.862 (1.236–2.805)	0.003
PLT counts ≤ 154*10^9/L	4.000 (1.610–9.938)	0.003
TKI-chemo	5.884 (3.922–8.827)	0.000
Overall survival		
Male	2.162 (1.278–3.732)	0.005
TKI-chemo	2.993 (1.754–5.108)	0.000
patients who completed the second consolidation cycle ($n=197$)		
Disease free survival		
Male	1.700 (1.029–2.806)	0.038
WBC ≥ 95*10^9/L	1.670 (1.015–2.747)	0.044
PLT counts ≤ 154*10^9/L	4.383 (1.712–11.218)	0.002
P190	2.172 (1.260–3.745)	0.005
BCR-ABL1 level reduction <3-log after 2 consolidation cycles	1.876 (1.132–3.108)	0.015
TKI-chemo	5.884 (3.922–8.827)	0.000
Overall survival		
Male	1.888 (1.028–3.468)	0.040
P190	2.304 (1.133–4.684)	0.021
TKI-chemo	3.259 (1.660–6.399)	0.001

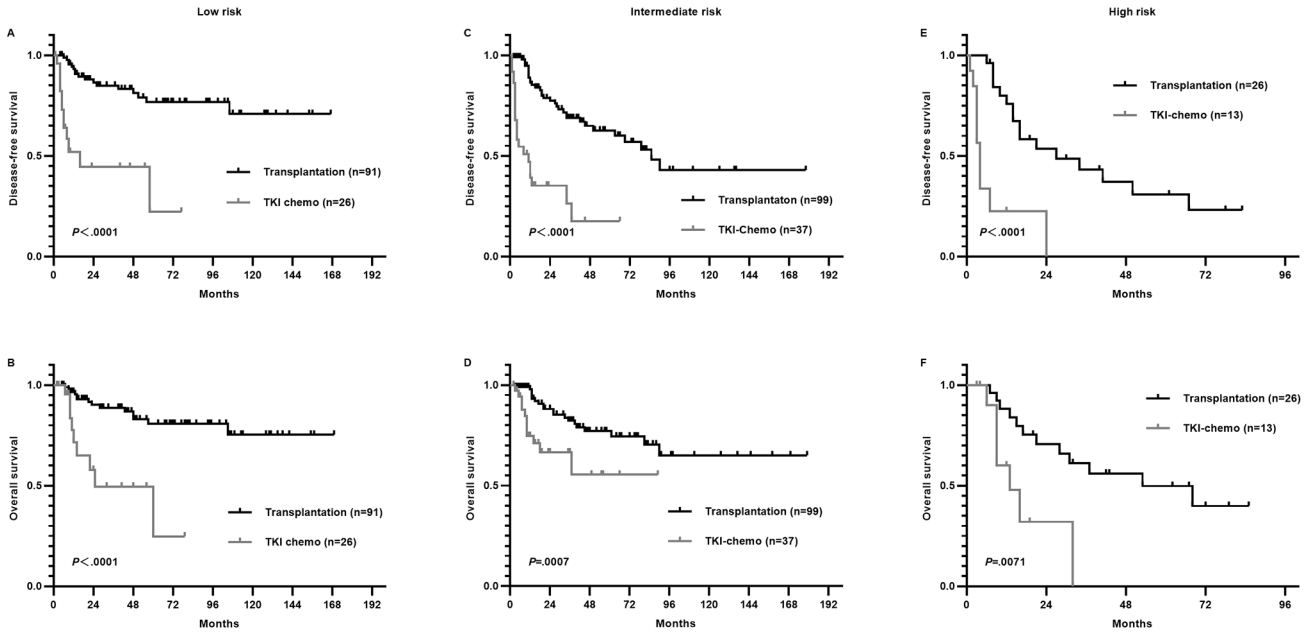

Fig. 2 Outcomes in the transplantation and TKI-chemo groups in 3 subgroups according to the risk factors

count ≥ 95 × 10^9/L, PLT count ≤ 154 × 10^9/L, P190, *BCR-ABL1* gene level reduction < 3-log after the second consolidation and not undergoing transplantation were significantly associated with poorer DFS (Table 2). Furthermore, in a prognosis analysis of 197 patients in low-risk groups with 0 or 1 risk factor, the transplantation group still had better DFS and OS than the TKI-chemo group.

Assessment of the role of transplantation in the subgroups

Considering the imbalance in baseline characteristics between the transplantation and TKI-chemo groups, we performed PSM analyses to assess the role of transplantation (Table 3).

Table 3 Patient unadjusted characteristics before PSM

the whole cohort			
	Transplantation (*n* = 216)	**TKI-chemo (*n* = 76)**	***P* value**
Gender:			0.669
Male	117 (54%)	44 (58%)	
Female	99 (46%)	32 (42%)	
Age, median (range)	35 [14; 64]	48 [21; 63]	< 0.001
WBC, × 10^9/L median (range)	38 [1; 488]	52 [2; 443]	0.284
Hemoglobin, g/L median (range)	103 [11; 187]	106 [35; 165]	0.813
Platelet, × 10^9/L median (range)	48 [1; 403]	40 [4; 310]	0.302
Blasts in BM, % median (range)	88 [21; 98]	91 [22; 99]	0.019
older than 49-year old			
	Transplantation (*n* = 33)	**TKI-chemo (*n* = 32)**	***P* value**
Gender:			0.266
Male	13 (40%)	18 (56%)	
Female	20 (61%)	14 (44%)	
Age, median (range)	54 [50; 64]	55 [50; 63]	0.421
WBC, × 10^9/L median (range)	45 [2; 399]	48 [3; 443]	0.684
Hemoglobin, g/L median (range)	107 [11; 165]	120 [5; 165]	0.231
Platelet, × 10^9/L median (range)	57 [5; 403]	59 [6; 224]	0.328
Blasts in BM, % median (range)	85 [21; 98]	92 [22; 97]	0.103
younger than 50-year old			
	Transplantation (*n* = 183)	**TKI-chemo (*n* = 44)**	***P* value**
Gender:			0.918
Male	104 (57%)	26 (59%)	
Female	79 (43%)	18 (41%)	
Age, median (range)	33 [14; 49]	37 [21; 49]	0.075
WBC, × 10^9/L median (range)	36 [1; 488]	52 [2; 365]	0.288
Hemoglobin, g/L median (range)	102 [38; 187]	90 [35; 164]	0.274
Platelet, × 10^9/L median (range)	46 [1; 383]	39 [4; 310]	0.315
Blasts in BM, % median (range)	88 [21; 98]	91 [24; 99]	0.088
patients achieved CMR after 1 consolidation cycle			
	Transplantation (*n* = 84)	**TKI-chemo (*n* = 26)**	***P* value**
Gender:			0.741
Male	44 (52%)	12 (46%)	
Female	40 (48%)	14 (54%)	
Age, median (range)	35 [17; 64]	51 [21; 61]	< 0.001
WBC, × 10^9/L median (range)	34 [2; 456]	23 [2; 443]	0.286
Hemoglobin, g/L median (range)	114 [48; 187]	109 [61; 165]	0.838
Platelet, × 10^9/L median (range)	51 [4; 403]	46 [4; 183]	0.303
Blasts in BM, % median (range)	88 [21; 98]	90 [24; 98]	0.240
patients not achieved CMR after 1 consolidation cycle			
	Transplantation (*n* = 132)	**TKI-chemo (*n* = 50)**	***P* value**
Gender:			0.372
Male	73 (55%)	32 (64%)	
Female	59 (45%)	18 (36%)	
Age, median (range)	35 [14; 62]	43 [21; 63]	0.002
WBC, × 10^9/L median (range)	43 [1; 488]	79 [3; 365]	0.053
Hemoglobin, g/L median (range)	93 [11; 169]	87 [35; 164]	0.853
Platelet, × 10^9/L median (range)	46 [1; 297]	40 [6; 310]	0.643
Blasts in BM, % median (range)	88 [21; 98]	91 [22; 99]	0.054
patients achieved CMR after 2 consolidation cycles			
	Transplantation (*n* = 70)	**TKI-chemo (*n* = 12)**	***P* value**
Gender:			0.438
Male	29 (41%)	7 (58%)	
Female	41 (59%)	5 (41.67%)	

Table 3 (continued)

Age, median (range)	38 [14; 64]	52 [24; 60]	0.018
WBC, × 10^9/L median (range)	31 [1; 456]	23 [4; 443]	0.813
Hemoglobin, g/L median (range)	105 [11; 158]	90 [63; 154]	0.515
Platelet, × 10^9/L median (range)	49 [3; 403]	45 [6; 183]	0.479
Blasts in BM, % median (range)	88 [21; 98]	91 [65; 98]	0.131
patients not achieved CMR after 2 consolidation cycles			
	Transplantation ($n=95$)	**TKI-chemo ($n=20$)**	***P* value**
Gender:			0.920
Male	61 (64%)	12 (60%)	
Female	34 (36%)	8 (40%)	
Age, median (range)	34 [14; 62]	40 [22; 63]	0.066
WBC, × 10^9/L median (range)	46 [1; 488]	58 [6; 349]	0.647
Hemoglobin, g/L median (range)	101 [38; 165]	115 [37; 164]	0.404
Platelet, × 10^9/L median (range)	46 [1; 250]	40 [14; 310]	0.779
Blasts in BM, % median (range)	86 [26; 98]	9 [22; 98]	0.167

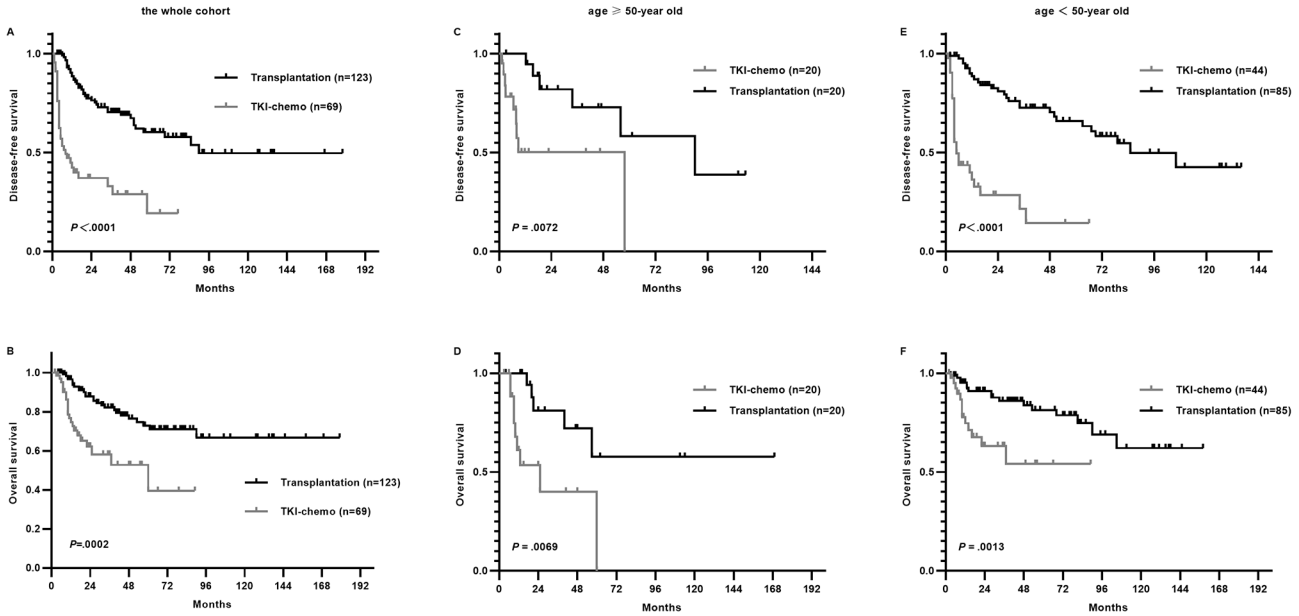

Fig. 3 Outcomes in the transplantation and TKI-chemo after propensity matching score by all patients (A-B) and age (C-H).

All patients

After PSM according to a 2:1 ratio, 123 patients from the transplantation group and 69 patients from the TKI-chemo group were well balanced (Supplementary Table 2). The 4-year DFS (47% vs. 21%, $P<.001$) and OS rates (77% vs. 51%, $P<.001$) in the transplantation group were higher than those in the TKI-chemo group (Fig. 3A-B).

By age

Because age has a well-known association with outcome in patients who undergo transplantation, we performed PMS analysis in 65 patients older than ($n=65$, according to a 1:1 ratio) or younger than ($n=227$, according to a 2:1 ratio) 50 years of age. The 4-year DFS and OS rates in the transplant cohorts were significantly higher than those in the TKI-chemo groups (Fig. 3C-F).

By *BCR-ABL1* level

After completing the first consolidation cycle, 110 patients achieved CMR, including 91 patients with undetectable *BCR-ABL1* transcripts. After PSM analysis among CMR patients, the 4-year DFS rate in the transplantation group ($n=32$, 80%) was higher than that in the TKI-chemo group ($n=23$, 44%, $P=.010$); however, there was no significant difference in OS rate (86% vs. 66%, $P=.225$) (Fig. 4A-B).

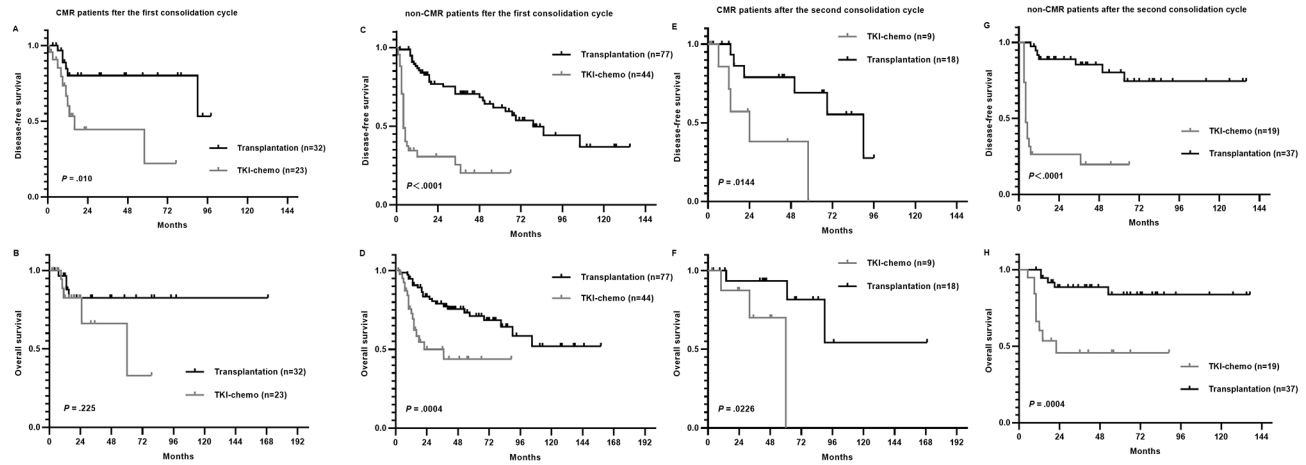

Fig. 4 Outcomes in the transplantation and TKI-chemo after propensity matching score by *BCA-ABL1* gene levels after the first (**A-D**) and second consolidation (**E-H**).

According to PSM analysis among non-CMR patients, both the 4-year DFS and OS rates were better in the transplantation group (Fig. 4C-D). In addition, among 197 patients who completed the second consolidation, 82 patients achieved CMR (70 patients in the transplantation group, 12 patients in the TKI-chemo group). PSM analysis was performed in CMR patients and non-CMR patients, and those who received transplants had better 4-year DFS and OS rates than those who received TKIs with chemotherapy (Fig. 4E-H).

Discussion

In the current study, we found that transplantation was superior to imatinib or dasatinib plus chemotherapy in patients with Ph+ALL younger than 65 years old regardless of *BCR-ABL1* level. Our findings suggest that transplantation remains a one-time cure for this disease among young adults in regions lacking accessibility to third-generation TKIs or immunotherapies.

In previous studies, when comparing imatinib or dasatinib plus chemotherapy with transplantation, the 3-5-year DFS and OS rates were 28–43% vs. 48–63% and 35–50% vs. 56–60%, respectively. In the ponatinib plus chemotherapy and allo-HSCT groups, the 3-year OS rate was 87% vs. 70% [9, 11, 15, 16]. Ghobadi et al. compared outcomes of those who did and did not receive allo-HSCT in first remission and found that allo-HSCT was not associated with improved 3-year relapse-free survival rates (62% vs. 54%, $P = .15$) [30]. In our study, the median ages of the transplantation and TKI plus chemotherapy groups were 35 vs. 48 years, and the 4-year DFS and OS rates were 68% vs. 24% and 72% vs. 47%, respectively. The OS rates were similar to those of other reported studies. The transplantation group had seemingly better DFS rates, but the chemotherapy group had poorer DFS rates than previously reported studies. A number of reasons can explain this discrepancy. First, the patients in the transplant group were younger, with a median age of 35 years, and may reflect better tolerance during the HSCT process. Second, the majority of transplants were from haploidentical donors in our study, which had previously been confirmed to have a stronger GVL effect than HLA-matched donors [14]. Third, TKI-chemo patients did not choose transplantation, perhaps due to poor physical conditions and economic reasons, which also contributed to poorer chemotherapy outcomes. At present, in China, one treatment cycle of the 3rd generation TKIs olverembatinib, blinatumomab and inotuzumab ozogamicin costs approximately 14,000, 250,000 and 200,000 RMB, respectively, and none of them can be affordable. In addition, there were no differences between imatinib or dasatinib subgroups in our current analysis. Consistent with published data, chemotherapy combined with imatinib or dasatinib also led to similar survival rates ranging from approximately 40-50% [7, 31].

Published studies have suggested that with the use of TKI combined with chemotherapy, a 3-log reduction in *BCR-ABL1* after remission can reduce the relapse incidence and improve the survival rate, the latter of which can also be achieved with CMR at 3 months. Recently, several studies reported that the decision to perform transplantation should depend on the reduction in *BCR-ABL1* level during treatment [9, 11, 15, 16]. However, we found that the transplantation group had better DFS rates than the TKI plus chemotherapy group even though *BCR-ABL1* was not detected after the first and second consolidation chemotherapies. As previously described, one of the main reasons was that the patients in the transplantation group were younger and typically received transplants from

haploidentical donors in our study. Of course, in the future, the addition of third-generation TKIs or novel immunotherapy may further improve the efficacy among those who do not undergo allogeneic transplantation.

Among the limitations, this was a retrospective study, and importantly, patients were not randomized to receive TKIs and chemotherapy or transplants, instead, the choice of therapy was left to the patients' preference. There was an obvious difference in the number of patients in the HSCT and chemotherapy groups, with substantially more patients in the former. In addition, there was also a difference in baseline data between the two groups that could not be corrected despite the use of PSM. It is worth considering that third-generation TKIs as well as immunotherapy can further improve the outcomes of Ph+ALL patients in the future. However, in developing countries, the widespread use of third-generation TKIs and immunotherapy remains limited. The main reason for the shorter follow-up period in the non-transplant cohort was that median OS duration was shorter in the non-transplant cohort rather than that many of the non-transplant patients transferred to another hospital during the treatment.

We conclude that transplantation, as a one-time procedure for adults with Ph+ALL, remains important in the era of TKIs in countries lacking accessibility to third-generation TKIs or immunotherapy, regardless of the depth of the molecular response. This conclusion still needs to be verified through randomized studies with larger sample sizes.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing financial interests.

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