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RESEARCH ARTICLE

Superiority of allogeneic hematopoietic stem cell transplantation to nilotinib and dasatinib for adult patients with chronic myelogenous leukemia in the accelerated phase

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Abstract **In the tyrosine kinase inhibitor (TKI) era, imatinib is the first-line therapy for patients with chronic myeloid leukemia (CML) in chronic or accelerated phase. Although second-generation TKIs (TKI_2), including dasatinib and nilotinib, are appropriate treatment regimens for patients with disease that progressed to accelerated phase following imatinib therapy, allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the only curative therapy. This study retrospectively analyzed the efficacy of TKI_2 and HSCT for treatment of CML in accelerated phase. Ninety-three patients with CML registered in the Chinese CML alliance database from February 2001 to February 2014 were enrolled and divided into the TKI_2 ($n = 33$) and allo-HSCT ($n = 60$) groups. In the TKI_2 group, 26 and 7 patients received nilotinib and dasatinib, respectively, as initial TKI_2 and 11 patients transferred to the alternative TKI_2 after failure to one TKI_2. In the allo-HSCT group, 22 (36.7%), 35 (58.3%), and 3 (10%) patients underwent allo-HSCT from an HLA-matched sibling donor, HLA mismatched/haploidentical donor, and unrelated donor, respectively. All patients in the HSCT group were engrafted. Overall, 69.7%, 48.5%, and 45.5% of patients presented hematological, cytogenetic, and major molecular responses, respectively, to at least one of TKI_2. All 60 patients (100%) achieved CHR and cytogenetic response in the HSCT group. Patients in the TKI_2 group exhibited lower 5-year overall survival rate (42.9% vs. 86.4%, $P = 0.002$), 5-year event-free survival rate (14.3% vs. 76.1%, $P < 0.001$), and 5-year progression-free survival (28.6% vs. 78.1%, $P < 0.001$) than those in the allo-HSCT group. Multivariate analysis showed that male sex and TKI_2 therapy were predictors of poor overall survival, whereas hemoglobin < 100 g/L and TKI_2 therapy were predictors of poor event-free survival and progression-free survival. These results indicated that allo-HSCT may be superior to nilotinib and dasatinib for adult patients with CML in accelerated phase.**

Keywords chronic myeloid leukemia; imatinib; dasatinib; nilotinib; allogeneic hematopoietic stem cell transplantation

Introduction

Chronic myeloid leukemia (CML), a common malignant disorder of hematopoietic stem cells, comprises three phases: chronic, accelerated, and blast. Accelerated phase (AP) describes patients presenting certain signs of disease progression without meeting the criteria for blast phase [1]. AP-CML is associated with poor median survival, ranging from 6 to 24 months, and generally leads to rapid fatal blast phase [1,2]. As advances in CML therapy with tyrosine kinase inhibitors (TKIs) have considerably improved patient survival, the role of allogeneic hematopoietic stem cell transplantation (allo-HSCT) has become less important, particularly for patients with CML in chronic phase [3]. However, HSCT remains the only proven curative therapy for patients with CML in advanced stages, including AP [4,5].

Jiang [6] compared the first-generation TKI imatinib mesylate with allo-HSCT and reported that HSCT is the optimal treatment for selected patients with AP-CML. By

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contrast, the National Comprehensive Cancer Network recommends TKI as the first-line treatment [7]. Hence, the choice of therapy for AP-CML remains controversial.

Second-generation TKIs (TKI_2), including nilotinib and dasatinib, can induce faster and stronger molecular responses and may achieve better overall survival (OS) and progression-free survival (PFS) than first-generation TKIs [8–11]. Meanwhile, human leukocyte antigen (HLA)-mismatched/haploidentical HSCT, has greatly progressed and yielded clinical results that are comparable with that of matched sibling HSCT [12–15]. Currently, almost every patient can have a donor [16]. We recently reported that haploidentical HSCT provides a 4-year OS rate of 73.3% for AP-CML [17]. However, the efficacy of TKI_2 has not been compared with that of HSCT. Therefore, this study retrospectively analyzed data from the Chinese CML alliance database to compare the efficacy of TKI_2 and HSCT for the treatment of AP-CML.

Materials and methods

Patients

Data were obtained from the Chinese CML alliance database from February 2001 to February 2014. The inclusion criteria were as follows: 18–65 years of age, diagnosis of AP-CML according to the WHO 2001 classification criteria [7], adequate performance status (Eastern Cooperative Oncology, Group 0–2), and starting TKI_2 therapy or under preparative conditioning during the study period. Patients were excluded if they had any severe infection or pulmonary, cardiac, liver, or renal diseases. Patients who began TKI_2 treatment for AP-CML were assigned to the TKI_2 group ($n = 33$), whereas patients in AP or second chronic phase at the time of transplantation were assigned to the HSCT group ($n = 60$). Informed consent was obtained from all patients prior to inclusion in the study.

Therapy

Nilotinib and/or dasatinib

Of 33 patients in the TKI_2 group, 31 patients were resistant or intolerant to imatinib and the 2 remaining patients received nilotinib as the first-line therapy. Patients were orally administered with nilotinib at 400 mg b.i.d. or dasatinib at 100–140 mg daily. Dose reduction or interruption was allowed in cases of toxicity. Cautious re-administration of nilotinib at 400 mg twice daily or dasatinib at 100 mg daily was permitted when adverse events abated to a severity of grade 1 or less and in cases with lack of response or persistent disease.

Fourteen patients who received nilotinib were enrolled in the Novartis-expanded nilotinib access phase IIIb study between February and December 2007, whereas 12 patients who received dasatinib were enrolled in the Bristol-Myers Squibb phase II study (clinical protocol: CA180160) between February and November 2008. All patients were followed up until the end of October 2014.

Allo-HSCT

For patients in the HSCT group, the transplantation conditioning protocol was performed as described previously [12,14,15]. In brief, donor stem cells from bone marrow or peripheral blood stem cells (PBSCs) were mobilized with recombinant human G-CSF. In HLA-matched or HLA-mismatched sibling/haploidentical transplantation, G-CFS-primed bone marrow and PBSCs were not manipulated and infused fresh. In the unrelated donor transplantation, PBSCs were infused. A combination of cyclosporine, mycophenolate mofetil, and short-term methotrexate was administered for acute graft-versus-host disease (GVHD). Steroids and/or second-line immunosuppressants were also used to manage GVHD.

All patients were followed up until the end of October 2014.

Cytogenetic and molecular analyses

Cytogenetic analysis was performed using the G-banding technique. Bone marrow specimens were examined on direct short-term (24-h) cultures, and at least 20 metaphases were analyzed. The BCR-ABL transcripts were detected by analyzing bone marrow through nested reverse-transcriptase polymerase chain reaction (PCR) before 2005 and quantitative real-time PCR after 2005. The normalization ratios of the BCR-ABL transcripts in the quantitative PCR analysis were obtained by comparison with the ABL transcripts [18]. BCR-ABL domain mutations were analyzed as previously reported [19].

Patients who received TKI_2 therapy were evaluated for hematologic, cytogenetic, and molecular responses at frequent intervals. Hematologic response was analyzed weekly for the first 3 months and monthly thereafter. Cytogenetic and molecular responses were analyzed every 3 months for the first 6 months and every 6–12 months thereafter.

Patients who received HSCT therapy underwent serial measurements of the BCR-ABL transcript levels in bone marrow at 1, 2, 3, 6, 9, 12, 18, and 24 months after transplantation and annually thereafter. Immunosuppressant withdrawal and imatinib therapy or modified donor lymphocyte infusion were used to treat disease relapse [20,21].

Response criteria and outcome definitions

Hematological response included complete hematologic response (CHR) and was defined as no evidence of leukemia and return to chronic phase (CP_2) [7]. Cytogenetic (MCyR/CCyR) and molecular responses were defined according to the criteria in the NCCN guideline [7].

OS was defined as the time from the start of TKI therapy (TKI_2 patients) or HSCT (HSCT patients) to all-cause mortality or final follow-up. Event-free survival (EFS) was defined as the time between the commencement of treatment (i.e., TKI_2 or allo-HSCT) and the appearance of any of the following events: absence of hematologic response at 3 months; loss of previously obtained CHR, major cytogenetic response, or complete cytogenetic response; post-transplant molecular relapse; relapse in AP or blast phase; or death from any cause. Molecular relapse was defined as positive BCR-ABL transcripts confirmed by two consecutive assays after previously achieving complete molecular response (CMR) or a persistent BCR-ABL transcript increase of more than 1-log. In the allo-HSCT group, relapse was defined as relapse in any form, including hematologic, cytogenetic, and molecular relapses. PFS was defined as the time from the beginning of treatment to a relapse in AP or blast phase. In the allo-HSCT group, relapse included hematologic, cytogenetic, and molecular relapses.

Statistical analysis

Differences between groups were tested using the Mann-Whitney *U*-test for continuous variables and χ^2 for categorical variables. Kaplan-Meier method was used to assess statistical significance in time-to-event analyses. Univariate and multivariate analyses were performed to determine the factors predictive of OS, EFS, and PFS. Log-rank test was used to identify prognostic factors. Factors with $P < 0.2$ were included as variables in the Cox regression model. The level of significance was set at $P < 0.05$. All statistical analyses were performed with SPSS version 13.0 (SPSS, Inc., Chicago, IL, USA).

Results

Patient characteristics

A total of 93 patients were enrolled, including 33 patients in the TKI_2 group and 60 patients in the HSCT group. The baseline characteristics of the patients are shown in Table 1. The allo-HSCT group presented significantly high platelet count ($P = 0.003$), long AP period ($P = 0.003$), and long follow-up ($P < 0.001$). Meanwhile, the TKI_2 group demonstrated significantly long CML course ($P = 0.003$) and long median duration of exposure to imatinib therapy ($P < 0.001$).

In the TKI_2 group, two patients received nilotinib as first-line therapy, 17 switched from imatinib to TKI_2 after progression to the AP stage, and 14 switched to TKI_2 because of failure to imatinib during AP. Domain mutations, including Y253H, T315I, M244V, L384M, L248R, G250E, E255V, and E255K, were identified in eight patients before nilotinib administration. Meanwhile, mutations, including Y253H, E255K, and Y253H, were

Table 1 Baseline characteristics ($n = 93$)

	TKI_2 group	HSCT group	*P* value
n	33	60	
Median age (year)	39 (20–65)	36 (18–61)	0.095
Sex (male/female)	25/8	40/20	0.251
CP/AP at first diagnosis of CML	25/8	45/15	0.572
Duration of CML (month)	33 (0–183)	9.5 (2–180)	0.013
Time since first diagnosis of AP (month)	0 (0–60)	4.5 (1–72)	0.003
Features at diagnosis of AP			
Splenomegaly diagnosis, *n* (%)	17 (51.2)	33 (55)	0.350
WBC median (range) ($\times 10^9$/L)	13.46 (0.99–520)	20.5 (1.0–280)	0.152
BPC median (range) ($\times 10^9$/L)	322 (40–2201)	900 (28–3000)	<0.001
Blasts in peripheral blood (%)	2 (0–13)	2 (0–18)	0.435
Bone marrow blasts (%)	5 (0–19)	6 (0–18)	0.89
PBa (%)	10 (0–43)	7 (0–34)	0.784
Clonal evolution, *n* (%)	3 (9.1)	5 (8.3)	0.760
Prior TKI therapy, *n* (%)	31 (93.9)	50 (83.3)	0.144
Duration of imatinib therapy (month)	17 (2–60)	3 (0.3–58)	<0.001
Follow-up (month)	22 (2.5–92)	82 (1–160)	<0.001

Data are presented as median (range) unless specified otherwise. Abbreviations: TKI_2, second-generation tyrosine kinase inhibitor; HSCT, hematopoietic stem cell transplantation; AP, accelerated phase; CP, chronic phase; CML, chronic myeloid leukemia; WBC, white blood cell.

identified in three patients before dasatinib administration.

In the HSCT group, 10 TKI-naïve patients received HSCT during AP as first-line therapy. Fifty patients received imatinib for a median of 3 months (range: 0.3–58 months) before HSCT. Patients were transplanted because of progression to AP under imatinib therapy ($n = 8$), received HSCT in AP or return-to-chronic phase because of imatinib failure ($n = 17$), or received scheduled HSCT within 5 months of imatinib because of intolerance or refusal to receive TKI for a long time ($n = 25$). Patients received HSCT in the third chronic phase ($n = 1$), second chronic phase ($n = 24$), or AP ($n = 35$).

Clinical outcomes

TKI_2 group

A total of 33 patients were included in the TKI_2 group. The initial TKI_2 regimen included nilotinib ($n = 26$) and dasatinib ($n = 7$). Among the patients who received nilotinib as initial TKI_2, 65.4% (17/26), 46.2% (12/26), 30.8% (8/26), and 30.8% (8/26) of the patients presented CHR, MCyR, CCyR, and MMR responses, respectively. Ten patients switched to dasatinib because of the absence of response ($n = 3$) or failure to respond to nilotinib ($n = 7$) after a median period of 18 months (range: 2–30 months). Of these patients, 4 patients had no any response to dasatinib and progress to blast phase within 1–4 months; 4 patients presented CHR, MCyR, and CHR CCyR as their best response but they lost previous response after 38, 12, 3, and 48 months; and 2 patients exhibited CMR and MMR responses with dasatinib as the alternative TKI_2 for 24 and 65 months. Among the 7 patients who received dasatinib as initial TKI_2, 57.1% (4/7), 42.9% (3/7), 42.9% (3/7), and 14.3% (1/7) of the patients presented CHR, MCyR, CCyR, and MMR responses, respectively. One patient switched to nilotinib after 2 months because of the absence of response to dasatinib, received 3 months of CHR without cytogenetic response, and then progressed to blast phase. Overall, 69.7%, 48.5%, and 45.5% of the patients demonstrated hematologic, cytogenetic, and MMR responses to at least one of TKI_2.

In the TKI_2 group, 12 patients died as a result of disease progression. Among the 21 surviving patients, 15 patients were alive without progression, 1 patient received salvage HSCT after returning to chronic phase from blast phase with the T315i mutation, 2 patients were alive in blast phase, and 3 patients were alive in second AP_2 with various domain mutation.

Allo-HSCT group

Of 60 patients who received HSCT, 22 (36.7%), 35 (58.3%), and 3 (10%) patients underwent allo-HSCT from an HLA-matched sibling donor, HLA mismatched/haploidentical donor, and an unrelated donor, respectively. Furthermore, 12, 6, and 42 patients received PBSCT, bone marrow, and both, respectively.

All patients achieved engraftment after HSCT. A total of 29 (48.3%) patients developed acute GVHD (10, 14, and 5 patients with grades I, II, and III/IV, respectively). Of the 59 patients who survived after more than 3 months, 24 (40.7%) developed chronic GVHD, including 11 and 13 with limited and extensive GVHD, respectively.

Seven patients received TKI or modified donor lymphocyte infusion as preemptive therapy according to the BCR-ABL levels after HSCT before hematological relapse or therapy after hematological relapse.

Among the 10 patients who died, 7 patients died from transplantation-related mortality, 1 patient received a second HSCT because of minimal residual disease and pancytopenia and then subsequently died from GVHD, and 2 patients died from relapse. The 50 remaining patients were alive at the final follow-up, in which 49 achieved CMR and 1 was alive in AP and received interferon-γ.

The status of patients at the end of follow-up time is listed in Table 2.

Comparison of survival between the TKI_2 and allo-HSCT groups

Median OS time was significantly shorter in the TKI_2 group (22 months, range: 2.5–91 months) than that in the allo-HSCT group (82 months, range: 1–160 months). Five-

Table 2 Status at the final follow-up

	TKI_2 group	HSCT group	*P* value
n	33	60	
Alive, *n* (%)	21 (63.3%)	50 (83.3%)	0.031
Median (range) survival time (month)	28 (12–91)	89 (13–160)	<0.001
CHR, *n* (%)	15 (71.4%)	50 (100%)	<0.001
MCR, *n* (%)	12 (57.1%)	49 (98%)	<0.001
CCR, *n* (%)	10 (47.2%)	49 (98%)	<0.001
MMR, *n* (%)	9 (42.9%)	49 (98%)	<0.001
CMR, *n* (%)	5 (23.8%)	49 (98%)	<0.001

year OS rate was significantly lower in the TKI_2 group than that in the allo-HSCT group (42.9% vs. 86.4%, respectively, $P = 0.002$; Fig. 1A).

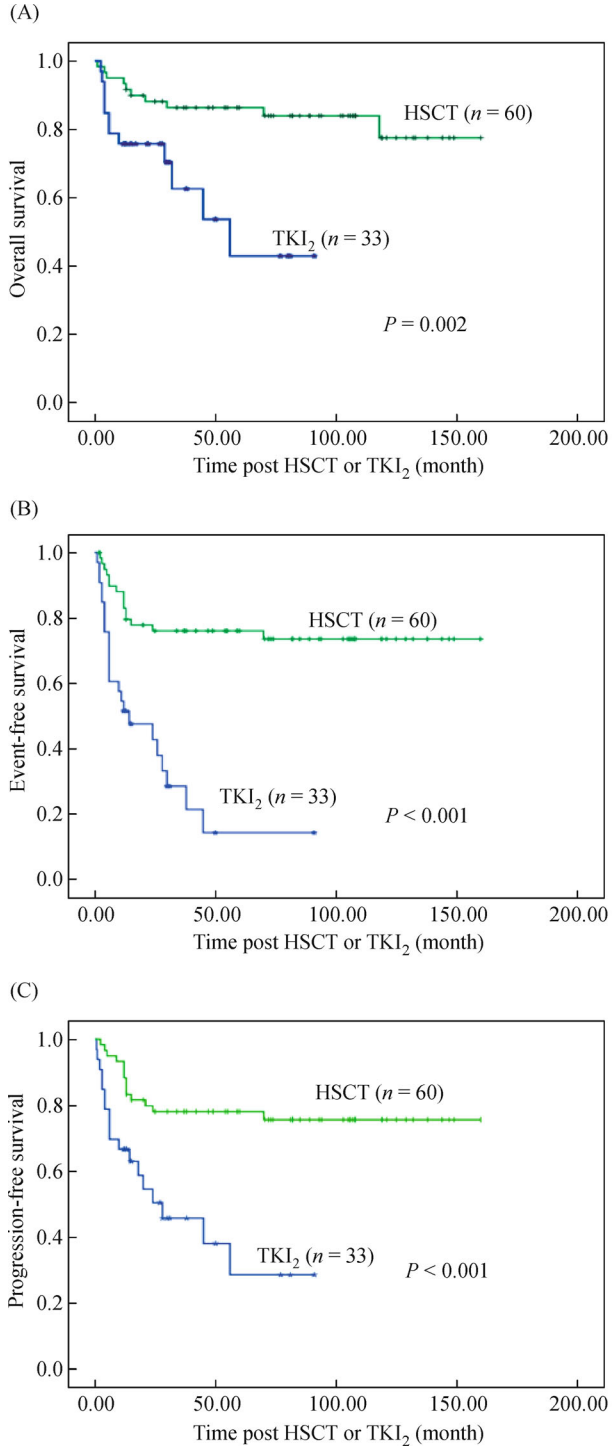

Fig. 1 Effect of different therapies on survival of patients with AP-CML. (A) Overall survival, (B) event-free survival, and (C) progression-free survival of patients with AP-CML with respect to therapy.

Median EFS time was significantly shorter in the TKI_2 group (12 months, range: 1.0–91.0 months) than that in the allo-HSCT group (70.25 months, range: 2–160 months). Five-year EFS rate was significantly lower in the TKI_2 group than that in the allo-HSCT group (14.3% vs. 76.1%, $P < 0.001$) (Fig. 1B).

Median PFS time was significantly shorter in the TKI_2 group (15 months, range: 0.3–91 months) than that in the allo-HSCT group (71.25 months, range: 2.3–160 months, $P < 0.001$). Five-year PFS rate was significantly lower in the TKI_2 group than that in the allo-HSCT group (28.6% vs. 78.1%, $P < 0.001$) (Fig. 1C).

Identification of prognostic factors

A total of 93 patients were included in univariate and multivariate analyses to identify predictors of OS and EFS. Univariate analysis showed that male sex and TKI_2 therapy were predictors of poor OS, whereas hemoglobin < 100 g/L and TKI_2 therapy were predictors of poor EFS and PFS (Table 3). These variables remained significant in multivariate analysis (Table 4).

Discussion

The NCCN guideline states that dasatinib, nilotinib, and bosutinib are appropriate treatment regimens for patients with CML that progressed to AP following TKI therapy; evaluation for allo-HSCT is also recommended on the basis of the response to TKI_2 therapy [7]. However, no evidence demonstrated that TKI_2 is more effective to HSCT for AP-CML. This work is the first study to compare the efficacy of allo-HSCT with TKI_2 for AP-CML. Our study showed that allo-HSCT is more effective than TKI_2 in terms of survival and cytogenetic or molecular response.

Le Coutre *et al.* [8] reported that for patients with AP-CML and resistance or intolerance to imatinib, the hematological response rate to nilotinib was 47%, the major cytogenetic response rate was 29%, and the 12-month OS rate was 79%. Among 137 patients with at least 24 months of follow-up, the hematological response rate was 55%, CHR was 31%, MCyR was 32%, and CCyR was 20%. The estimated PFS and OS rates at 24 months were 70% and 33%, respectively [9]. Guihot *et al.* [10] reported the results of the clinical trial, in which dasatinib was administered to 107 patients with AP-CML with imatinib resistance or intolerance. At a minimum of 8 months of follow-up, the OS, MaHR, and CHR rates were 81%, 64%, and 39%, respectively. Meanwhile, MCyR was 33% and CCyR was 24%. About 76% of patients were estimated to be alive and progression-free at 10 months. Follow-up of the full cohort of 174 patients confirmed the efficacy of dasatinib in imatinib-resistant or imatinib-intolerant

Table 3 Univariate analysis of factors associated with OS, EFS and PFS

Variable	*n*	OS		EFS		PFS	
		5-year OS	*P*	5-year EFS	*P*	5-year EFS	*P*
Total	93	74.3		57.8		64.4	
Age (year)							
<40	57	65.6	0.692	52.0	0.232	67.7	0.181
⩾40	36	89.8		61.3		58.2	
Sex							
Male	65	68.3	0.029	53.1	0.209	54.8	0.072
Female	28	92.4		67.7		78.6	
CML duration (month)							
<12	44	58.8	0.375	60.1	0.201	64.3	0.334
12–24	15	86.7		72.0		79.4	
>24	34	77.4		43.5		52.3	
IM time (month)							
No	12	81.5	0.534	72.9	0.246	0.815	0.273
0.3–7	44	80.3		60.5		65.3	
>7	45	62.9		42.4		48.5	
WBC count ($\times 10^9$/L)							
<18	44	80.8	0.382	57.6	0.986	61	0.785
⩾18	49	57.6		56.7		67.5	
Hb (mg/L)							
<100	33	68.7	0.121	47.8	0.037	51.5	0.020
⩾100	60	80.8		63.7		70.6	
BPC ($\times 10^9$/L)							
100–1000	53	74.0	0.981	58.9	0.434	69.4	0.404
<100 or>1000	40	74.7		56.5		61.1	
BM blasts (%)							
<10	72	76.7	0.263	54.3	0.72	63	0.686
10–19	21	71.4		66.7		58	
Splenomegaly							
No	41	79.7	0.276	58.1	0.887	71.2	0.252
Yes	52	61.3		57.7		59.6	
Ba in PB (%)							
<20	74	77.1	0.751	56.8	0.317	63.5	0.342
⩾20	19	69.6		61.5		64.2	
AP course							
⩾6 months	33	68.9	0.327	49.4	0.230	70.8	0.323
<6 months	60	80.4		62.4		52.8	
Therapy group							
HSCT	60	86.4	0.002	76.1	<0.001	78.1	<0.001
TKI_2	33	42.9		14.3		28.6	

Abbreviations: IM: imatinib mesylate; WBC: white blood cell; AP: accelerated phase; PB: peripheral blood.

Table 4 Multivariate analysis of factors associated with OS, EFS and PFS

Variable	OS			EFS			PFS		
	RR	95% CI	*P*	RR	95% CI	*P*	RR	95% CI	*P*
TKI_2	3.711	1.489–9.247	0.005	5.097	2.532–10.262	<0.001	3.673	1.774–7.605	<0.001
Male sex	3.484	1.016–11.946	0.047				2.237	0.912–5.492	0.071
Hb < 100 g/L				0.417	0.212–0.821	0.011	0.434	0.214–0.882	0.021

Abbreviations: OS, overall survival; EFS, event-free survival; PFS: progressive-free-survival; RR, relative risk; 95% CI: 95% CI for RR; TKI_2, second-generation tyrosine kinase inhibitor.

patients. The 12-month PFS and OS rates were 65% and 82%, respectively [11]. As most clinical outcomes were reported from 6 to 24 months [8–11], the response to TKI_2 may not be long lasting for patients with AP-CML. In the

present study, nilotinib as the initial TKI_2 therapy resulted in HR, MCyR, and CCyR rates of 54.6%, 46.2%, and 30.8%, respectively, and events occurred in 73.1% of patients, similar to the results of Le Coutre *et al.* [8].

The disease phase before transplantation remains an important factor in the TKI era, and survival remains poor for patients transplanted in AP. Gratwohl *et al.* [3] reported the survival rate of such patients to be 40%–47%. In the subgroup analysis of the CML phase IV study by Geman [22], the 5-year OS rate after HLA-matched related HSCT was approximately 40% in patients in AP. In recent report from the Center for International Blood and Marrow Transplant Research [23], the disease-free survival rate after allo-HSCT was 26%–27% in patients with AP-CML. The outcomes in the present cohort group, with 5-year OS, EFS, and PFS rates of 86.4%, 76.1%, and 78.1%, respectively, are better than those in the previous study. These findings are also similar to those of our previous report. Jiang [6] reported 6-year OS, EFS, and PFS rates of 83.3%, 71.8%, and 95.2%, respectively, for 45 patients who received allo-HSCT. Huang [17] also presented an OS rate of 73.3% in 15 patients with AP-CML who received haploidentical HSCT.

Several factors may have contributed to our superior transplantation outcomes. First, our HSCT patients were relatively young, with a median age of 36 years. Our patients also received HSCT early, had a relatively short disease course, and good physical performance. Second, 35 of 60 patients received HSCT from haploidentical donors, which may have a stronger graft-versus-leukemia effect. Third, we employed a preemptive strategy instead of prophylaxis [19], regular monitoring of the BCR-ABL transcript post-transplantation through quantitative PCR, and individualized intervention based on the minimal residual disease level and dynamic changes; these strategies possibly decreased relapse rate and improved survival. Fourth, modified donor lymphocyte infusion, instead of traditional donor lymphocyte infusion, was applied for intervention, which may have increased the graft-versus-leukemia effect and safety [20,21]. Fifth, treatment with short-course TKI may be beneficial as a bridge to transplantation. Finally, our centers have ample experience in managing complications of allo-HSCT, with hundreds of cases annually, which may have led to the low transplantation-related mortality.

The major limitation of this study is the retrospective design, small number of patients, and heterogeneity. The high number of imatinib-resistant patients in the TKI_2 group may have contributed to poor outcomes. Otherwise, the clinical outcome may be better in the transplantation group if the patients received HSCT or TKI_2 during the corresponding period because of inferior supportive care in the past. Therefore, large prospective randomized controlled trials are required to confirm the present findings.

In conclusion, our results indicated that allo-HSCT may be superior to TKI_2 with respect to molecular response, PFS, EFS, and OS. Therefore, allo-HSCT should be recommended as the first choice for the treatment of patients with AP-CML, particularly for patients who were previously treated with imatinib. However, further study is necessary to confirm our findings.

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Compliance with ethics guidelines

Lanping Xu, Huanling Zhu, Jianda Hu, Depei Wu, Hao Jiang, Qian Jiang, and Xiaojun Huang declare no conflicts of interest. All procedures followed were performed in accordance with the ethical standards of the committees on human experimentation (institutional and national) and with the *Helsinki Declaration* of 1975, as revised in 2000 (5). Informed consent was obtained from all patients who were included in the study.

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