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ORIGINAL ARTICLE

Prognostic Factors and Clinical Outcomes in Patients with Blast Phase Chronic Myeloid Leukemia

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SUMMARY

Background: **Given the low incidence of patients with advanced chronic myeloid leukemia (CML), comprehensive clinical characteristics and outcomes of cohort studies of patients diagnosed with blast phase chronic myeloid leukemia (BP-CML) are limited. We examined the clinical features of blast phase CML, including the TKI selection, treatment response, and whether they have had hematopoietic stem cell transplantation (HSCT) or not.**
Methods: **We performed a retrospective cohort study, including BP-CML patients diagnosed in our center from January 2013 to December 2022. Clinical features, treatment therapy, and overall survival (OS) were investigated.**
Results: **Out of the 11 patients, 2 were myeloid type, eight patients were B-lymphoid, and one was T-lymphoid. Four patients suffered from chromosome abnormalities. Four patients were identified with BCR-ABL1 kinase domain mutation, including T315I, E255K, M244v, and E279K. The overall CR, CRi, PR, and MLFS rates were 9%, 54%, 27%, and 9%, respectively. The median follow-up was 21 months (9.5 - 33 months). At the end of the follow-up time, seven patients died. CML patients with lymphoids tended to get a better OS than patients with a type of myeloid, but the difference was not statistically significant ($p > 0.05$). Patients who received HSCT had an improved OS by two years compared to those who had not received HSCT.**
Conclusions: **The prognosis of BP-CML patients was poor. Given the rarity of BP-CML and the limitation of clinical trial data, large-scale multi-center prospective studies are urgently needed to confirm and improve the treatment of patients with BP-CML in the future.**
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INTRODUCTION

Chronic myeloid leukemia (CML) is now under a relatively favorable prognosis with an incidence rate of 0.7 - 1.0/100,000 [1]. Only a minority of patients progressed to the aggressive blast stage with a very dismal prognosis, which may be myeloid, lymphoid, or mixed phenotype [2,3]. Chronic myeloid leukemia (CML) is characterized by a translocation of chromosomes 9 and 22, which leads to the formation of the Philadelphia chromosome (Ph). It produces the oncogene fusion protein BCR-ABL1 and a dysregulation of tyrosine kinase ac-

tivity [4].

The symptoms of CML in the chronic phase (CP) are usually related to anemia, recurrent infections, bleeding tendency, splenomegaly, unexplained emaciation, and night sweats [5]. With first-generation TKI approval (imatinib), it revolutionized the treatment landscape of chronic myeloid leukemia (CML) and improved the prognosis of CML patients and their quality of life. Second-generation TKIs (dasatinib, nilotinib, and bosutinib) and third-generation TKIs (olverembatinib and ponatinib) are also approved for front-line use; the incidence of chronic myeloid leukemia (CML), which has progressed to the accelerated phase (AP) or blast phase (BP), has decreased through them from more than 20% per year to between 1% and 1.5% per year [3,6]. Unfortunately, the median survival time of BP-CML is just 6 - 12 months [7]. It continues to be a clinical challenge to predict BP-CML progression and to treat patients with BP effectively. Given the low incidence of patients with advanced CML, most studies are case reports, and comprehensive clinical characteristics and outcomes of the patients diagnosed with BP-CML cohort study are insufficient. We examined the clinical features of blast phase CML, including the TKI selection, treatment response, and whether they have had transplantation or not.

MATERIALS AND METHODS

Participants and treatment

The present study included 11 adult patients with BP-CML from 2008 to 2022. BP-CML is defined as when 30% or more of the blasts are present in the peripheral blood or bone marrow with a prior diagnosis of chronic myeloid leukemia [8]. All patients signed informed consent, and the ethics committee reviewed the charts in our cohort study.

CML patients in blast crisis are usually treated with TKI combined with chemotherapy and a hematopoietic stem cell transplantation (HSCT) as soon as possible after returning to the chronic phase. Cytarabine, daunorubicin, fludarabine, idarubicin, and granulocyte colony-stimulating factor (G-CSF) are often used to induce the remission of acute myeloid leukemia. Cyclophosphamide, vincristine, doxorubicin, and dexamethasone combined with dasatinib are commonly used to remission lymphoid-type blasts. Patients in the blast phase with a T315I mutation should receive third-generation TKI (ponatinib). Laboratory data, including blood routine tests, coagulation function, liver and kidney function, myocardial enzymes, β2-microglobulin, serum ferritin, C-reactive protein, and Epstein-Barr virus DNA polymerase chain reaction testing, were acquired from the electronic medical records. Bone marrow cytology was further tested.

Response

The AML European Leukemia Network (ELN) 2022 criteria were used to evaluate the efficacy [9]. Complete remission (CR) was defined as < 5% bone marrow blasts, absence of circulating blasts, absence of extraordinary disease, neutrophil (ANC) > 1 x 10^9/L, and platelet count > 100 x 10^9/L. CR with partial hematologic response (CRh) was defined as ANC > 1.5 x 10^9/L, platelet count > 50 x 10^9/L, and all other CR criteria met. CR with incomplete hematologic response (CRi): ANC < 1 or platelet count < 100, meeting all other CR criteria. The definition for a morphologic absence of leukemic symptoms (MLFS) was less than 5% bone marrow blasts, absence of circulating blasts, absence of extraordinary disease, and a lack of exceptional symptoms and hematologic recovery. Partial remission (PR) response was confirmed when the percentage of bone marrow blasts dropped from 5% to 25%. The percentage of bone marrow blasts decreased to 50% after treatment.

Statistical analysis

The overall survival (OS) time was calculated from the initial treatment to either death at the last follow-up or the end of the follow-up. Relapse-free survival (RFS) was calculated from the response date to hematologic relapse, death, or the end of the follow-up. The Kaplan-Meier method and Log-rank test were used for survival analysis. Statistical analysis was done by using the software package R (http://www.R-project.org) and Empower Stats (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA, USA).

RESULTS

Baseline characteristics

Eleven patients with blast phase chronic myeloid leukemia were registered in our study, including seven male patients and four female patients. The median age at diagnosis with BP-CML was 41 years. Two CML patients translated to myeloid, while nine patients were lymphoid. The clinical characteristics of the BP-CML patients at baseline are shown in Table 1. Four patients suffered from chromosome abnormalities. The conversion time from the chronic phase to the blast crisis was 80.0 (23.0, 114.0) months. The median bone marrow blasts of the white blood cells were 74.0 (43.5, 88.2). Among them, four patients were detected with BCR-ABL1 kinase domain mutation, including T315I, E255K, M244v, and E279K, and two patients had it combined with leukemia of the central nervous system. Six patients were treated with the TKI inhibitor dasatinib combined with chemotherapy. All patients received TKI therapy. The summary of the responses and type of front-line treatments for BP-CML are shown in Table 2. The overall CR, CRi, PR, and MLFS rates were 9%, 54%, 27%, and 9%, respectively.

Individual patient characteristics, treatment responses, and outcomes are presented in Table 3. All patients had

Table 1. Clinical characteristics of patients with Ph+ AML and CML in blast phase (BP).

Characteristics	n (%)
Gender	
Male	7 (64)
Female	4 (36)
Age	41.0 (34.0, 55.5)
ECOG performance 0 - 2	9 (82)
Type of blast phase	
AML	2 (18)
B-ALL	8 (73)
T-ALL	1 (9)
Complex cytogenetics	4 (36)
Time from diagnosis of CML to blast phase (months)	80.0 (23.0, 114.0)
Bone marrow blasts, %	74.0 (43.5, 88.2)
BCR-ABL1 kinase domain mutation	
T315I	1 (9)
E279K	1 (9)
M244v	1 (9)
E255K	1 (9)
No mutations	7 (64)
Central nervous system leukemia	2 (18)
Prior regimens for CML	
Prior TKI exposure	11 (100)
Prior venetoclax	0 (0)
Initial TKI for blast phase	
Imatinib	1 (9)
Dasatinib	6 (54)
Orebatinib	1 (9)
Nilotinib	1 (9)
Ponatinib	2 (18)
Non TKI	0 (0)
Laboratory data	
WBC (x 10^9/L)	4.1 (2.3, 14.8)
Platelet (x 10^9/L)	110.0 (36.0, 168.0)
Hemoglobin (g/L)	95.0 (70.5, 112.0)
Albumin (g/L)	40.9 (38.6, 45.8)
Lactate dehydrogenase (U/L)	304.0 (188.0, 398.0)
Triglyceride (mmol/L)	1.7 (1.3, 2.5)
Fibrinogen (g/L)	2.9 (2.2, 3.3)
Ferritin (ng/mL), n = 22	884.2 (484.4, 1,956.0)

an evaluative response. Only one patient (1/11) achieved the criteria for complete remission (CR), seven patients achieved CR with incomplete hematologic recovery (CRi), one patient (9%) achieved a morphologic leukemia-free state (MLFS), and three patients (27%) had a partial response. Among them, five patients suffered a relapse within one year, and two patients died within nine months. According to the type of TKI, the distribution of patients was as follows: dasatinib in 5 (5/11) patients, imatinib in 1 (1/11) patient, orebatinib

Table 2. Summary of responses and type of frontline treatments for BP-CML.

Initial treatment	Event (%)	% Response			
		CR	CRi	PR	MLFS
TKI alone	1 (9%)	0	1	0	0
TKI with chemotherapy	10 (91%)	1	5	3	1
Non-TKI	0 (0)	0	0	0	0
TKIs used for BP-CML					
Imatinib	1 (9%)	9	-	-	-
Dasatinib	6 (54%)	9	36	9	-
Orebatinib	2 (18%)	-	-	9	-
Nilotinib	1 (9%)	-	-		-
Ponatinib	1 (9%)	9	-	9	9

CR - complete remission, Cri - incomplete remission, PR - partial remission, MLFS - morphology showed no symptoms of leukemia, BP-CML - chronic myeloid leukemia in blast phase, TKI - tyrosine kinase inhibitor.

in 1 (1/11) patient, nilotinib in 1 (1/11) patient, and ponatinib in 2 (2/11) patients.

The median follow-up was 21 months (9.5 - 33 months). At the end of the follow-up time, seven patients had died. The prognoses of the 11 patients are shown in Figure 1. The conversion time from chronic phase to blast crisis in CML patients was divided into two groups (< 12 months, ≥ 12 months). Patients with less than 12 months of conversion time had all died within one year (Figure 1A). CML patients with lymphoids tended to have a better OS than patients with a myeloid, but the difference was not statistically significant (Figure 1B). Patients with ABL1 mutations had no significant difference in OS than patients without ABL1 mutations (Figure 1C). Patients who received HSCT had an improved OS by two years compared to the patients who did not receive HSCT (Figure 1D).

DISCUSSION

With the introduction of TKI therapy, the incidence of accelerated phase CML has been dramatically reduced [10]. Most patients had died within one year after progressing to BP-CML. Therefore, the prognosis and survival of patients are significantly affected by the occurrence of the blast phase [5]. Due to its rarity, previous research has focused chiefly on case reports, clinical trials, and expert opinions. This retrospective study aimed to examine the disease's clinical features, treatment responses, and prognosis factors.

TKI has significantly improved the survival time of CML patients, but the BP-CML patients' outlook remains hopeless [11]. Patients during the use of TKI received ph+-targeted TKI along with chemotherapy or immunotherapy regimens, with intensive induction therapy for myeloid BP and a vincristine and prednisolone-based multiagent approach for lymphoid BP. Nine patients (9/11) of the BP-CML patients were lymphoid, while only two myeloid patients (2/11) were included in our study. This was much higher than in the 2016 revision of the World Health Organization classification [12]. The outcome of patients with myeloid BP is worse than that of those with lymphoid BP [13]. The results of our study show that patients with lymphoid BP have a longer total survival time than those with myeloid BP. In a retrospective study, it was determined that TKI coupled with intensive chemotherapy (IC) or HMA leads to an elevated response rate and lessens the risk of a relapse [14]. This combination therapy approach improved the 5-year survival OS compared with TKI alone, suggesting that the optimal treatment for patients with BP-CML is to combine IC or HMA with TKI instead of using TKI alone [14]. In our study, only 1 (1/11) patient received TKI therapy alone, and that patient underwent a stem cell transplant after an induced remission. After 32 months of follow-up, there were no signs of disease recurrence or progression in that patient. A recent cohort study of 477 patients conducted by Jain et al. [15] has pinpointed the clinical features that are related to a poor OS or an increased risk of treatment failure. Those poor prognostic factors include age > 58 years, lactate dehydrogenase level > 1,227 IU/L, platelet count < 102 x 10^9L, no history of stem cell transplantation, transition to BP from chronic phase to accelerated phase, and the presence of chromosome 15 aberrations. Our study did not demonstrate any significant improvement in patients' overall survival time after receiving HSCT. It is interesting to note that the chance of a two-year OS for patients with HSCT was higher than for those who did not receive HSCT. The three-year OS in patients with BP-CML who received HSCT after BP-CML remained poor, as was reported by Khoury et al. [10].

Table 3. Characteristics and outcomes of individual patients with blast phase CML.

	Age (years)	Gender	Blasts (%)	Blastic type	Interval time (months)	Ph+ %	ABL mutation	Treatment	Response	HSCT	Relapse	Outcomes
1	36	male	83.5	T-lymphoid	34	NA	Neg	Imatinib + HA	CR	no	no	alive
2	23	female	89.5	B-lymphoid	108	62	Neg	Dasatinib + VICP	CRi	no	yes	alive
3	40	female	74	B-lymphoid	35	55	E279K	Dasatinib + VIP	CRi	yes	yes	died
4	32	female	94	B-lymphoid	80	60	Neg	Dasatinib + VP	CRi	yes	yes	died
5	56	male	95	B-lymphoid	181	98	Neg	Dasatinib	CRi	yes	no	alive
6	27	male	44	Myeloid	108	78	Neg	Orebatinib + HA	PR	no	yes	died
7	41	male	87	B-lymphoid	5	93	Neg	Dasatinib + VIP	PR	no	yes	died
8	55	male	37	B-lymphoid	120	NA	M244v	Nilotinib + VDP	CRi	yes	yes	died
9	59	male	52	B-lymphoid	7	60	T315I	Ponatinib + CVP	MLFS	yes	no	alive
10	53	female	37	B-lymphoid	12	23	E255K	Dasatinib + VICP	CRi	yes	no	alive
11	58	male	59	Myeloid	121	32	Neg	Ponatinib + HA	PR	yes	yes	died

CR - complete remission, Cri - Complete remission with incomplete hematologic response, PR - partial remission, HA - homoharringtonine + cytosine arabinoside, VICP - vindesine + idarubicin + cyclophosphamide + dexamethasone, VIP - vindesine + idarubicin + dexamethasone, VP - vindesine + dexamethasone, VDP - vindesine + daunorubicin + dexamethasone, CVP - cyclophosphamide + vincristine + prednisone. Interval time, patients with CML from chronic phase to blast crisis phase.

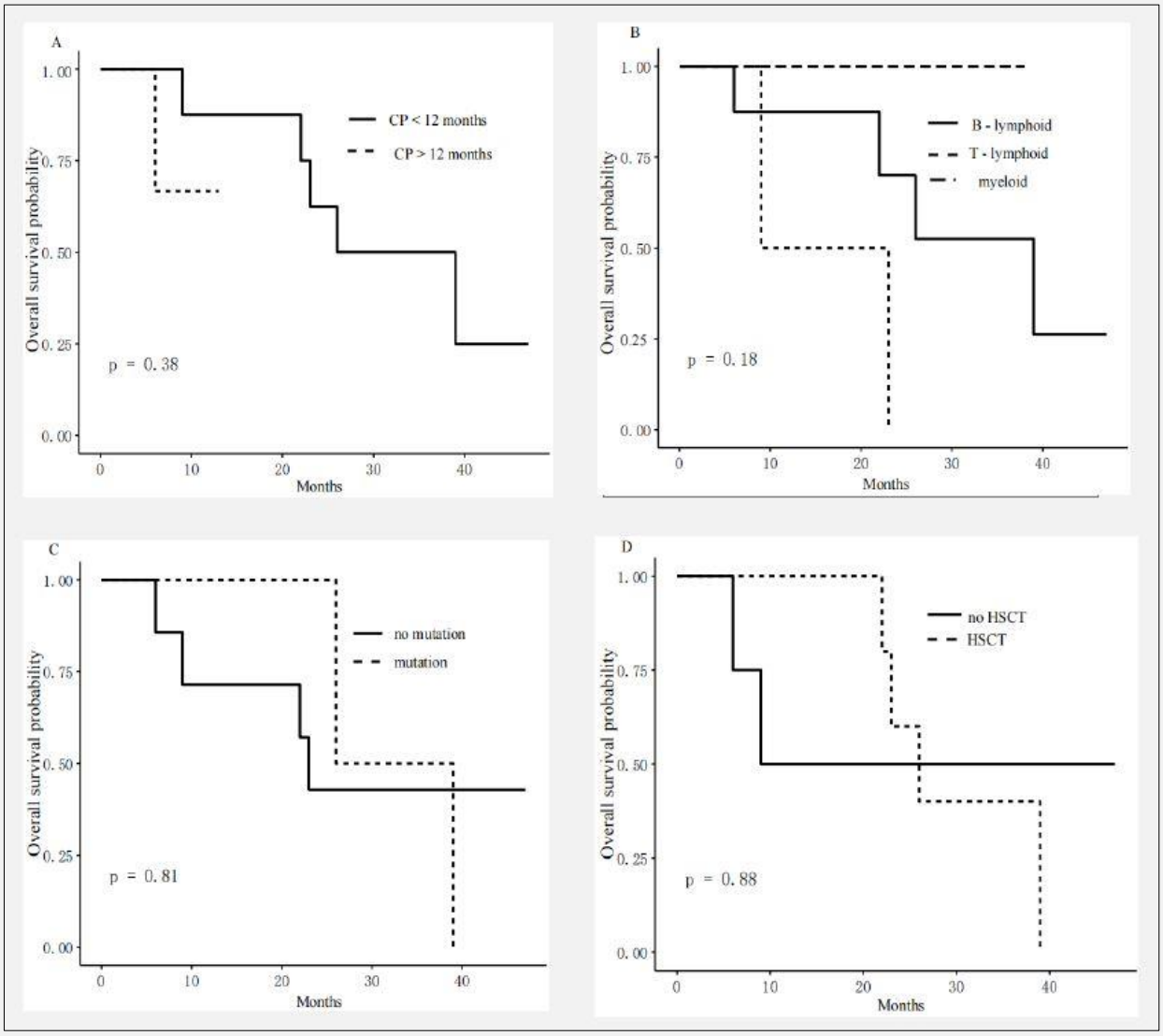

Figure 1. Overall survival in patients with chronic myeloid leukemia in blast phase (BP-CML).

Comparison of overall survival based on (A) conversion time from CP to BP, (B) type of BP, (C) ABL mutation, and (D) hematopoietic stem cell transplantation (HSCT).

Lyczek et al. [16] reported that nearly 70% of CML relapse patients are accompanied by mutations in the Bcr-Abl kinase domain and that a point mutation of the Abl kinase domain gene causes P210 Bcr-Abl protein kinase to reactivate, which is believed to be a significant cause of drug resistance. Furthermore, interfering with the drug's binding to the target by directly blocking imatinib's binding to Abl kinase or blocking Abl kinase inactivation and conformation eventually leads to drug resistance [17]. Mutations of Bcl-Abl kinase have been regarded as independent predictors of loss of complete cytogenetic response (CCyR) and disease progression. In recent years, several studies have suggested that Bcl-Abl mutations are associated with disease progression and recurrence, and the most common types of mutations included M244V, Y253H, F359C/V/I, G250E, E255K, and T315I [18,19]. Our current report identified four patients (36%) with ABL1 mutations who had previously been treated with TKIs and were E279K, M244v, T315I, and E255K. The OS showed no statisti-

cal differences between patients with the Bcl-Abl kinase mutation and those without it. This difference may be due to a limitation of the sample size.

Up to date, there is a lack of standard criteria for treatment. After introducing TKIs, the incidence of BP-CML was significantly reduced, especially with second and third-generation inhibitors for the treatment [20]. In our study, 5 (45%) patients have died within two years, demonstrating a poor prognosis. Data from a cohort study indicated a median survival of only 12 months [14]. In our current analysis, all patients were treated with TKIs. Six patients used dasatinib for treatment, and 5 (80%) patients achieved CRi. Dasatinib is effective for treating CML patients resistant to imatinib due to its ability to overcome resistance to most BCR-ABL mutations [21]. Cortes et al. demonstrated that dasatinib could effectively generate complete hematologic and cytogenetic responses in patients resistant or intolerant to imatinib [22]. We were unable to draw conclusions about the efficacy of different TKIs due to the small number of patients treated with the same TKI in our cohort study. The efficacy of second-generation TKI in treating BP-CML needs to be further investigated in future large-scale prospective studies.

Our analysis remains with several limitations. This study was a single-center retrospective cohort study and involved a relatively small number of patients. We could not assess the effect of TKI alone versus TKI combined with chemotherapy on the treatment response. Data on chromosomal abnormalities, such as complex karyotypes, and molecular factors, such as TP53, ASXL1, KMT2D, TET2 mutations, etc., were not analyzed.

CONCLUSION

In conclusion, BP-CML is a rare disease, and although most patients can benefit from TKI treatment, the prognosis is still poor, which poses a challenge for clinicians. The results of this study indicate that the overall prognosis of lymphoid BP is better than that of the patients with myeloid BP. The results demonstrated that the two-year survival time differs between patients with HSCT and those without HSCT. Hematopoietic stem cell transplantation may lead to better outcomes. Given the rarity of BP-CML and the limitation of the clinical trial data, large-scale multi-center prospective studies are urgently needed to confirm and improve the treatment of BP-CML in the future.

Declaration of Interest:

All authors declare no conflict of interest.

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