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Original Article

Clinical Features and Treatment Outcomes of 51 Patients with Chronic Myeloid Leukemia Treated with a Tyrosine Kinase Inhibitor at a Single Institution from 2002 to 2014

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Although clinical trials of first- and second-generation tyrosine kinase inhibitors (TKIs) have been shown to improve the prognosis of chronic myeloid leukemia (CML), there is still uncertainty about the clinical features, treatment outcomes, adverse effects, and other possible problems of their use in the clinical setting. We retrospectively analyzed 51 CML patients treated with TKIs at a single institution between 2002 and 2014. The patients (median age: 53.8 years) were classified as having chronic (n = 48), accelerated (n = 2), or blastic phase (n = 1) CML. Our treatments included both 1st generation TKIs (60.8%) and 2nd generation TKIs (39.2%). We found that the overall response rates of complete cytogenetic response (CCyR), major molecular response (MMR), and MR4 (molecular response 4) were 90.2%, 78.4%, and 64.7%, respectively. Second line 2nd generation TKIs had response rates equivalent to those of 1st line 1st generation TKIs. Moreover, 1st line 2nd generation TKIs tended to achieve an early response rate. Overall survival (OS) at 5 years was 93.2%. Sudden blastic crisis (BC) occurred in 2 CML patients receiving TKI with CCyR status. Hematopoietic stem cell transplantation was performed for BC (n = 1) and sudden BC (n = 2). Side effects of all grades (1-3) and grade 3 alone were 64.7% and 11.8%, respectively. Dose reduction, replacement with another TKI, or low dose TKI treatment may be useful methods to control side effects. Further reasons of TKI discontinuation were economic problems (n = 3) and pregnancy (n = 1). Consequently, our treatment strategy for CML demonstrated good response rate and OS. Currently, treatment discontinuation due to intolerance, resistance, economic problems, pregnancy, and sudden BC remains a concern in clinical practice. 〔*J Clin Exp Hematop 56(1):34-42, 2016*〕

Keywords: chronic myeloid leukemia, intolerance, resistance, 1st & 2nd generation tyrosine kinase inhibitors

INTRODUCTION

Chronic myeloid leukemia (CML) is a hematological myeloproliferative disorder that is characterized by the Philadelphia chromosome.[1-3] The first generation BCR-ABL inhibitor, a type of tyrosine kinase inhibitor (TKI), has been shown to dramatically improve the treatment outcome of CML, with an overall survival (OS) of approximately 90% at 5 years.[4] However, an extended follow-up IRIS study showed that 30-40% of enrolled CML patients discontinued treatment due to intolerance or resistance to TKI therapy.[5] The latter subset of CML patients displayed poor clinical outcomes with an OS of only 50% at 5 years.[5] Recently, 2nd generation TKIs have been reported to improve the early treatment response and disease progression into accelerated phase (AP) or blastic crisis (BC).[6,7] However, the OS of CML patients treated with 2nd generation TKIs was found to be equal to that of those treated with 1st generation TKIs.[6,7] Moreover, the long term safety of 2nd generation TKI therapy has not been established.[6,7] Thus, it is unclear whether 1st or 2nd generation TKI therapy is more suitable for the initial treatment of CML.[4,6,7] The TARGET system study of 1st generation TKIs for treating patients with CML in Japan

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revealed that the clinical features and treatment outcomes of CML patients were similar to those found in the previous IRIS study.[8] Moreover, the available clinical data from Japanese CML patients, such as the subanalysis of the DASISION and ENESTnd clinical trials, which enrolled 49 and 79 Japanese CML patients, respectively,[9,10] also demonstrated the efficacy of 2nd generation TKI treatment. Although most physicians in Japan utilize 1st or 2nd generation TKIs in clinical practice, there have been no previous reports regarding the clinical features and treatment outcome of CML treated with 1st line 1st generation TKIs, 1st line 2nd generation TKIs, or 2nd line 2nd generation TKIs in the real-world setting. Thus, in the present study, we retrospectively analyzed CML cases in the clinical setting that were treated over the last 13 years with 1st or 2nd generation TKIs, focusing on the clinical features, treatment outcomes, adverse events, and social problems of 51 patients with CML at a single institution in Miyazaki.

PATIENTS AND METHODS

A total of 51 patients were diagnosed with CML at Miyazaki Prefectural Miyazaki Hospital between January 1, 2002 and December 28, 2014. According to the CML diagnostic criteria, we classified the 51 cases of CML into chronic phase (CP) (n = 48), AP (n = 2), or blastic crisis phase CML (n = 1).[11] At Miyazaki Prefectural Miyazaki Hospital, the treatment strategy for CML is based on CML subclassification, age, performance status, complication, and patient decision regarding therapy.[11] For CML patients in CP, we administered 1st generation TKI in the form of oral imatinib 400 mg QD (quaque die) between January 2002 and December 2011, and 2nd generation TKI in the form of oral dasatinib 100 mg QD or nilotinib 600 BID (bis in die) between January 2012 and December 2014. Strategies to control either adverse effects of TKI therapy or resistance to TKIs included dose reduction, dose escalation, or changing to another TKI. Efficacy was assessed according to the ELN 2006 definition.[11] Complete cytogenetic response (CCyR) was defined as the absence of Philadelphia chromosome in the bone marrow.[11] Molecular responses were assessed by quantitative reverse-transcriptase polymerase chain reaction (PCR) and converted to the International Scale (IS).[9] Major molecular response (MMR) was defined as a BCR-ABL transcript level in peripheral blood of IS < 0.1%.[9] MR4 was defined as a BCR-ABL transcript level in the peripheral blood of IS < 0.01%.[9]

The Sokal score was calculated as follows: Exp 0.01169 (age in years -43.4) + 0.03459 (spleen size -7.51) + 0.1889 ([platelet count/700]^2 -0.563) + 0.08879 (blast cell counts -2.10), where Exp is the exponential function. The Sokal risk scores were defined as follows: low Sokal risk (score < 0.8), intermediate (score 0.8–1.2), and high (score > 1.2).[12,13] The EUTOS score was calculated as follows: (7 × basophils) + (4 × spleen size) at diagnosis, with the spleen measured in centimeters below the costal margin, and basophils as a percentage ratio. An EUTOS score of > 87 indicated a high risk and ≤ 87 indicated a low risk.[14-16]

Safety was assessed and graded according to the Common Terminology Criteria for Adverse Effects version 3.0 of the National Cancer Institute.[11]

This retrospective study was conducted in compliance with good clinical practices and the ethical principles of the Declaration of Helsinki. Prior approval was obtained from the ethics review board at Miyazaki Prefectural Miyazaki Hospital.

The Kaplan-Meier method was used to estimate OS. The cumulative incidence was compared between CCyR, MMR, and MR4 using the log-rank test. Differences among variables of CCyR, MMR, and MR4 at 12 and 18 month were evaluated using Pearson's chi-square test. The relationship between risk stratification of Sokal scores and treatment response (CCyR and MMR) in 31 patients with CML treated with 1st generation TKIs was also evaluated using Pearson's chi-square test. A p-value < 0.05 was considered statistically significant.

RESULTS

Baseline characteristics of 51 CML patients treated with TKIs

According to the CML diagnostic criteria, the 51 CML patients were classified as having chronic (n = 48), accelerated (n = 2) or BC phase (n = 1) CML. The baseline characteristics of all patients are summarized in Table 1. The patient population included 27 men and 24 women, ranging in age from 20–86 years (median age: 53.8 years). Table 1 also shows the clinical features of the 1st generation TKI-treated patients, the 2nd TKI-treated patients, and patients treated with 2nd generation TKIs after first being treated with a 1st generation TKI (2nd line 2nd generation TKI group).

Clinical characteristics of TKI treatment

The initial treatment of the 51-patient cohort consisted of 1st generation TKI (imatinib) in 86.3% (44/51) of cases, and 2nd generation TKI (dasatinib or nilotinib) in 13.7% (7/51) of cases. Of the CML patients first treated with a 1st generation TKI, 13 patients were switched to a 2nd generation TKI, resulting in a final treatment ratio of 60.8% (31/51) 1st generation and 39.2% (20/51) 2nd generation TKI (dasatinib or nilotinib, respectively). In the 13 CML patients that required a switch from 1st generation to 2nd generation TKI, the reasons for the change were resistance (n = 11) and intolerance (n = 2) to the 1st generation TKI. Adverse effects of all

Table 1. Patient characteristics of 51 CML patients analyzed in this retrospective study

No. of case	N = 51 (Total)	N = 31 ①1st line 1st TKI	N = 7 ②1st line 2nd TKI	N = 13 ③2nd line TKI (1st TKI → 2nd TKI)
Sex	Male = 27 Female = 24			
Age (years)	53.8 (20-86)	55.9 ± 16.8 (Median 58)	47.4 ± 17.0 (Median 54)	52.4 ± 15.8 (Median 52)
Subclassification of CML	CP 48 AP 2 BP 1	CP 30 AP 0 BP 1	CP 6 AP 1 BP 0	CP 12 AP 1 BP 0
Sokal score	Low 29 Intermediate 13 High 9	Low 16 Intermediate 9 High 6	Low 7 Intermediate 0 High 0	Low 6 Intermediate 4 High 3
Eutos score	Low 49 High 2	Low 30 High 1	Low 7 High 0	Low 12 High 1
Laboratory findings (average ± SD)				
WBC (/mL)	53,913 ± 60,868	57,891 ± 51,592	29,856 ± 22,114	57,382 ± 85,310
Hb (mg/dL)	12.8 ± 2.5	12.4 ± 2.6	13.8 ± 1.5	13.8 ± 1.5
Plt (/mL)	$53.6 \times 10^4 \pm 43.7 \times 10^4$	$50.6 \times 10^4 \pm 38.1 \times 10^4$	$45.7 \times 10^4 \pm 18.7 \times 10^4$	$65.4 \times 10^4 \pm 59.2 \times 10^4$
LDH (IU/L)	637 ± 378	694 ± 366	444 ± 183	608 ± 427
Splenomegaly+	37 (73%)	25 (81%)	4 (57%)	8 (62%)
Splenomegaly-	14 (27%)	25 (81%)	3 (43%)	5 (38%)

N, number; CML, chronic myeloid leukemia; SD, standard deviation; WBC, white blood cell count; Hb, hemoglobin; Plt, platelet; LDH, lactate dehydrogenase

Table 2. Details of the observed adverse effects associated with tyrosine kinase inhibitor therapy in 51 chronic myeloid leukemia patients

Grades of adverse effect	No. of cases	Events
All grades	33 cases (64.7%)	
Grade 1-2	27 cases (52.9%) Imatinib: 22 cases Nilotinib: 5 cases	pancytopenia (15), peripheral edema (4), skin rash (3), glucose increase (5)
Grade 3	6 cases (5/51; 11.8%)	
	Imatinib: 2 cases	Skin rash
	Nilotinib: 1 case	Glucose intolerance
	Nilotinib: 1 case	Skin rash
	Dasatinib: 2 cases	Pleural effusion

Common Terminology Criteria for Adverse Effects grades for TKI therapy occurred in 64.7% of all cases (33/51) (Table 2). Grade 1-2 adverse effects were observed in 52.9% of the patients (27/51) and consisted of myelosuppression, peripheral edema, skin rash, and increased blood glucose levels, all of which were controlled and tolerated by the dose reduction. Grade 3 adverse effects were observed in 11.8% patients (6/51) and consisted of skin rash (imatinib: n = 2, nilotinib: n = 1), glucose intolerance (nilotinib: n = 1), and pleural effusion (dasatinib: n = 2).

Treatment response of 51 CML patients receiving TKI therapy

The final average doses of TKIs administered were 287 mg (range, 100-400 mg) of imatinib, 100 mg of dasatinib, and 522 mg (range, 300-800 mg) of nilotinib (Fig. 3). Final treatment responses are shown in Table 3. Final CCyR, MMR, and MR4 rates were 90.2%, 78.4%, and 64.7%, respectively. Rates of cumulative CCyR, MMR, and MR4 are shown in Fig. 1A. Rates of cumulative CCyR, MMR, and MR4 at one year were 66%, 32%, and 18%, respectively. Rates of CCyR, MMR, and MR4 were higher with clinical course in Fig. 1A.

Furthermore, we compared treatment response rates among 1st line 1st generation, 1st line 2nd generation, and 2nd line 2nd generation TKI groups (Table 3). Because most prior reports described response rates (CCyR, MMR, or MR4) at 3, 6, 12, or 18 mon,[8,9,10,15] we similarly compared CCyR, MMR, and MR4 at 3, 6, 12, and 18 mon. CCyR rates with 1st generation TKIs, 2nd generation TKIs, and 2nd line TKIs were 12.9%, 71.4%, and 23.1%, respectively, at 3 mon ($p = 0.004$); 35.5%, 100%, and 30.8%, respectively, at 6 mon ($p = 0.005$); 61.3%, 100%, and 53.9%, respectively, at

12 mon (p = 0.09); and 64.5%, 100%, 61.5%, respectively, at 18 mon (p = 0.308).

MMR rates were 3.2%, 14.3%, and 0%, respectively, at 3 mon (p =0.277); 6.5%, 85.7%, and 7.7%, respectively, at 6 mon (p < 0.001); 22.6%, 85.7%, and 25.0%, respectively, at 12 mon (p = 0.008); 38.7%, 85.7%, and 33.3%, respectively, at 18 mon (p = 0.008).

MR4 rates were 0%, 0%, and 0%, respectively, at 3 mon; 3.2%, 28.6%, and 0%, respectively, at 6 mon (p = 0.021); 6.5%, 66.8%, and 16.7%, respectively, at 12 mon (p = 0.08); 12.9%, 83.3%, and 16.7%, respectively, at 18 mon (p = 0.005) (Fig. 1B, 1C & 1D).

The response rates of the 2nd line 2nd generation TKI group (CCyR at 12 and 18 mon and MMR at 3 and 18 mon) were almost equivalent to those of the 1st generation TKI group despite the fact that the 2nd line 2nd generation TKI-treated group included 11 CML patients resistant to 1st generation TKIs. Moreover, the 1st line 2nd generation TKI group tended to achieve an earlier response, showing good response demonstrated by CCyR rate at 3 and 6 mon, MMR rate at 6 and 12 mon, and MR4 rate at 6,12, and 18 mon.

Treatment outcomes of 51 CML patients receiving TKI therapy

The treatment outcomes of the 51 CML patients treated with TKIs are shown in Fig. 3. The 5-year OS of CML was 93.7%. CML statuses of the four CML patients who died were sudden BC phase (n = 2), accelerated phase (n = 1), and chronic phase (n = 1). The causes of death were infection after hematopoietic stem cell transplantation (HSCT) (n = 2), pneumonia (n = 1), and aortic dissection (n = 1).

Treatment outcomes of HSCT in BC patients

HSCT was performed in one BC and 2 sudden BC patients (Table 4). The CML patient with BC was treated using 1st generation TKI combined chemotherapy plus HSCT; the patient attained complete remission without disease progression. Sudden BC occurred in 2 CML patients in CCyR during treatment with a 1st generation TKI. The duration of the sudden BC was 2 mon and 1 mon and the BC types were lymphoid crisis and myeloid crisis, respectively. The treatment for sudden BC was escalated doses of either 1st generation TKI plus HSCT or 2nd generation TKI plus HSCT. Consequently, the 2 sudden BC patients attained complete remission. However, both patients developed opportunistic infections, including either *pneumocystis pneumonia* or human herpesvirus 6 encephalitis, and died.

Prognostic factors of CML

Because Sokal and Eutos scores may be used as prognostic indicators,[12-15] we examined the association between response rate and Sokal scores in 31 CML patients treated with 1st generation TKIs. The Eutos score was not investigated because of the small number of high-risk patients. The 2nd generation TKI group and the 2nd line 2nd generation TKI group were also not examined because of their small sizes. Based on the risk stratification of the Sokal scores, the cumulative achievement of CCyR and MMR at 18 mon could be predicted by the Sokal scores (p = 0.02, p = 0.017) (Table 5).

Low dose TKI treatment in a dose-escalation manner

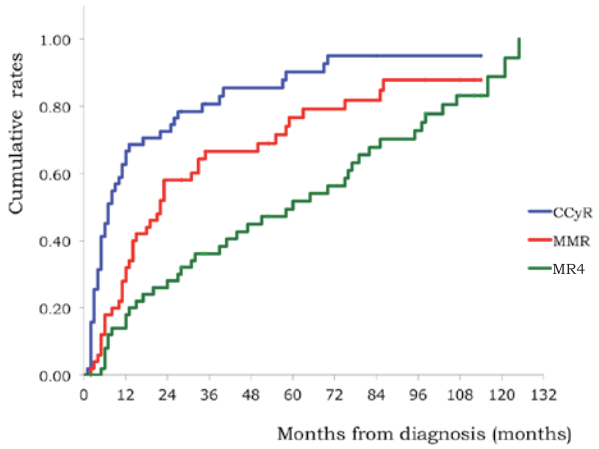
For 4 CML patients with intolerance to TKI therapy (grade 3) and 2 elderly CML patients with cardiovascular complications, we administered low dose TKI treatment in a dose-escalation manner (Table 6). In the 4 CML patients with intolerance to TKI, low-dose TKI was initiated, with eventual administration of the full dose of TKI with escalation, while in the 2 elderly CML patients with cardiovascular complication, low dose TKI was continued. These

Table 3. Treatment response of chronic myeloid leukemia patients to 1st and 2nd generation with tyrosine kinase inhibitor (TKI) therapy

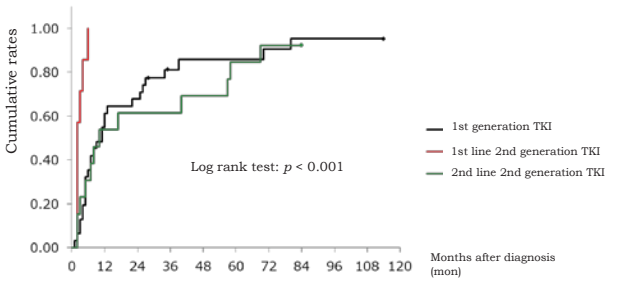
Treatment response (final)	No. of cases				
	1st line 1st TKI	2nd TKI (total)	1st line 2nd TKI	2nd line 2nd TKI (1st TKI → 2nd TKI)	Total
MR4	21	12	5	7	33 (64.7%)
MMR	24	16	7	10	40 (78.4%)
CCyR	27	19	7	12	46 (90.2%)
PCyR	3	1	0	1	4 (7.8%)
Non major CyR	1	0	0	0	1 (2%)

TKI, tyrosin kinase inhibitor; MR4, molecular response 4; MMR, major molecular response; CCyR, complete cytogenetic response; PCyR, partial cytogenetic response

1A

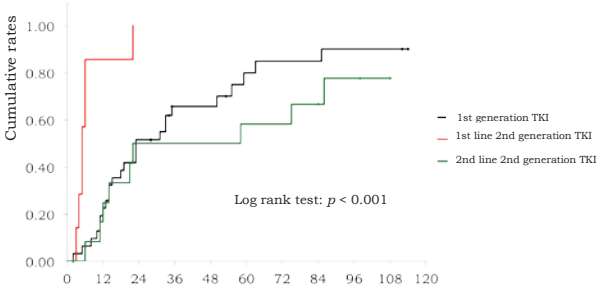


1B



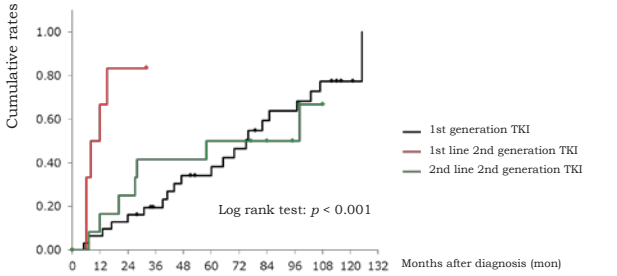
	The cumulative response rate at 3 mon (95% CI)	6 mon	12 mon	18 mon
1st line 1st generation TKI (IMA)	12.9% (3.6-29.8)	35.5% (19.2-54.6)	61.3% (44.1-78.4)	64.5% (47.7-81.4)
1st line 2ne generation TKI (NIL, DAS) (2GTKI)	71.4% (29.0-96.3)	100%	100%	100%
2nd line 2nd generation TKI (2nd TKI)	23.1% (5.0-53.8)	30.8% (9.1-61.4)	53.9% (26.8-81.0)	61.5% (35.1-88.0)
p value	$p = 0.004$	$p = 0.005$	$p = 0.09$	$p = 0.308$

1C



	The cumulative response rate at 3 mon (95% CI)	6 mon	12 mon	18 mon
1st line 1st generation TKI (IMA)	3.2% (0.1 -16.7)	6.5% (0.8 -21.4)	22.6% (7.9 -37.3)	38.7% (21.6-55.9)
1st line 2ne generation TKI (NIL, DAS) (2GTKI)	14.3% (0.4-57.9)	85.7%(42.1-99.6)	85.7% (59.8-100)	85.7% (59.8-100)
2ndline 2nd generation TKI (2nd TKI)	0%	7.7% (0.2-36.0)	25.0% (0.5-49.5)	33.3% (6.7-60.0)
p value	$p = 0.277$	$p < 0.001$	$p = 0.008$	$p = 0.08$

1D



	The cumulative response rate at 3 mon (95% CI)	6 mon	12 mon	18 mon
1st line 1st generation TKI (IMA)	0%	3.2% (0.1 -16.7)	6.5% (0 -15.0)	12.9% (1.1-24.7)
1st line 2ne generation TKI (NIL, DAS) (2GTKI)	0%	28.6% (3.7-71.0)	66.8% (29.0-100)	83.3% (53.5-100)
2nd line 2nd generation TKI (2nd TKI)	0%	0%	16.7% (0-37.8)	16.7% (0-37.8)
p value	-	$p = 0.021$	$p = 0.008$	$p = 0.005$

Fig. 1. Cumulative response rates. (***1A***) Cumulative response rates [Complete cytogenetic response (CCyR), major molecular response (MMR), MR4 (molecular response 4)] of chronic myeloid leukemia (CML) patients following tyrosine kinase inhibitor (TKI) therapy. (***1B***) Comparison of CCyR among the 1st line 1st generation TKI, 1st line 2nd generation TKI, and 2nd line 2nd generation TKI CML patient groups. (***1C***) Comparison of major molecular response among the 1st line 1st generation TKI, 1st line 2nd generation TKI and 2nd line 2nd generation TKI CML patient groups. (***1D***) Comparison of MR4 among the 1st line 1st generation TKI, 1st line 2nd generation TKI, and 2nd line 2nd generation CML patient groups. CI, confidence interval; IMA, imatinib; NIL, nilotinib; DAS, dasatinib

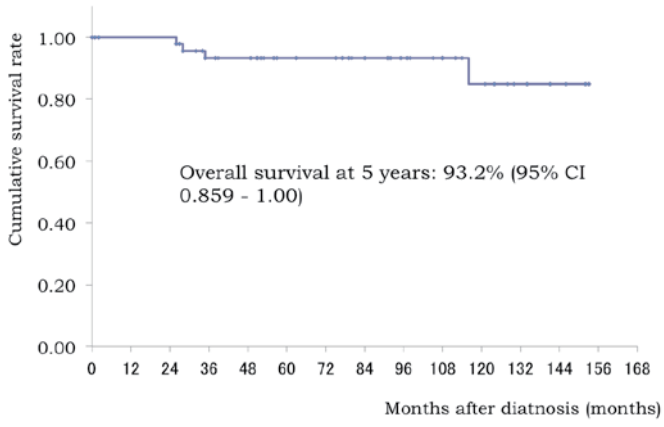


Fig. 2. Overall survival of 51 CML patients treated with final doses of tyrosine kinase inhibitor. CI, confidence interval

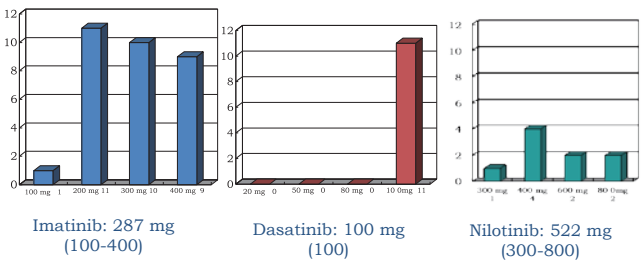


Fig. 3. Final doses of tyrosine kinase inhibitors used to treat CML patients

Table 4. Description of sudden blastic crisis observed in two chronic myeloid leukemia patients (CML) in this study

	Case 1	Case 2
Tyrosin kinase inhibitor	Imatinib	Imatinib
CML status before sudden blastic crisis	CCyR	CCyR
The duration from CCyR to sudden blastic crisis	2 mon	1 mon
Subtype of sudden blastic crisis	Lymphoid crisis	Myeloid crisis
Treatment	Escalated dose of imatinib plus HSCT	2nd TKI: nilotinib plus HSCT
Treatment outcome	2nd CR	2nd CR
Complication, cause of death	*Pneumocystis pneumonia*	Human herpesvirus-6 encephalitis

CCyR, complete cytogenetic response; HSCT, hematopoietic stem cell transplantation; CR, complete remission

Table 5. The relationship between risk stratifications of Sokal scores and treatment response (CCyR and MMR) in 31 chronic myeloid leukemia patients treated with 1st generation tyrosin kinase inhibitor

Sokal score	Number	CCyR at 12 mon	CCyR at 18 mon	MMR at 18 mon
Low	16 (52%)	81%	88%	69%
Intermediate	9 (29%)	44%	44%	11%
high	6 (19%)	33%	33%	0%
		(p = 0.057)	(p = 0.020)	(p = 0.017)

CCyR, Complete cytogenetic response; MMR, major molecular response

approaches achieved control of CML status with tolerable adverse effects.

Discontinuation of TKI due to reasons other than intolerance and resistance

Economic difficulties of patients (including 2 elderly patients) (n = 3), and pregnancy (n = 1) were critical social reasons for TKI discontinuation aside from the classic reasons of intolerance and resistance to TKI. Before discontinuation of TKI, the 4 CML patients had attained CCyR status. However, after the discontinuation of TKI, the molecular levels of the BCR-ABL transcript gradually progressed while in CCyR.

Minor BCR-ABL CML patient

A minor BCR-ABL CML case, with minor BCR-ABL fusion, was diagnosed by PCR analysis (Fig. 4). This patient was initially treated with a 1st generation TKI and responded well, attaining MR4 with negative findings of minor BCR-ABL fusion by PCR analysis and no further disease progression, despite the reported poor outcome of minor BCR-ABL CML in the literature.[16]

Comparison between our current study and previous reported clinical trials

The rates of treatment response, treatment outcome, and progression into AP or BC in our retrospective study were consistent with previously reported clinical trials.[8-10]

DISCUSSION

In this retrospective study including both 1st generation TKIs (60.8%) and 2nd TKIs (39.2%) for treating CML in a real-world setting, the rates of treatment response, treatment outcome, disease progression, and adverse effects in 51 CML patients treated with TKIs were analyzed and found to be consistent with those in three reported clinical trials (the TARGET system, DASISION, and ENESTnd studies).[8-10] Our study highlighted the current efficacy and challenges facing CML treatment with TKIs, namely the excellent response, good survival, the adverse effects (60%), intolerance (10%), and resistance to TKI therapy (21%), complications such as sudden BC during TKI treatment (2 cases), as well as social causes for the discontinuation of therapy including economic problems (3 cases) and pregnancy (1 case). These findings suggest that management of the latter clinical and social challenges may be essential to achieve optimal treatment response and outcomes for CML patients in clinical practice.

In our study, we had excellent efficacy demonstrated by excellent response and good survival rates that were consistent with previous reports, despite our including both 1st generation (60.8%) and 2nd generation TKIs (39.2%). Among two-thirds of the patients with CML, 1st generation TKIs showed good response and survival rates without any severe adverse effects, even when administered long-term. Moreover, in patients with CML treated with 1st generation TKIs, risk stratification by Sokal scores may be a useful tool for the prediction of the cumulative incidence of response (CCyR and MMR at 18 mon). However, 1/3 of our CML

Table 6. Clinical response of low dose tyrosin kinase inhibitor (TKI) treatment in dose escalation manner for 4 chronic myeloid leukemia (CML) patients who experienced adverse effects after initial treatment with a TKI and for 2 elderly CML patients with cardiovascular complication

Adverse effects of 1st treatment (1-4) The elderly + cardiovascular complications (5, 6)	1st treatment	2nd treatment	Progression of adverse effects	Final status of CML
1. Skin rash (grade 3)	Imatinib	Dasatinib	-	MR4
2. Skin rash (grade 3)	Imatinib	Dasatinib	-	MR4
3. Peripheral edema (grade 3)	Imatinib	Nilotinib	-	MR4
4. Pancytonenia (grade 3)	Imatinib	Nilotinib	-	MR4
5. The elderly + cardiovascular complications	Imatinib	-	-	CCyR
6. The elderly + cardiovascular complications	Imatinib	-	-	CCyR

MM4, complete molecular response; CCyR, complete cytogenetic response

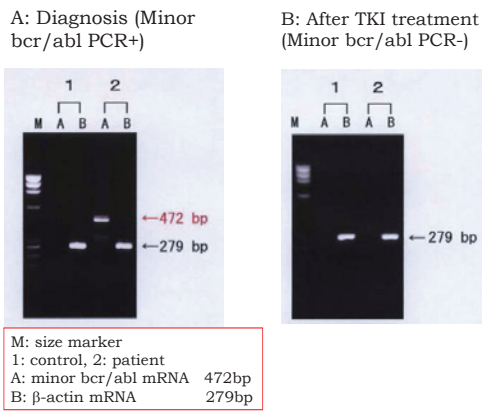


Fig. 4. Analysis of *BCR-ABL* mutation in a CML patient: identification of minor BCR-ABL fusion by polymerase chain reaction. PCR, polymerase chain reaction

patients were treated with 2nd generation TKIs. The 1st line 2nd generation TKI group achieved an earlier response, with strong response demonstrated by rates of CCyR at 3 and 6 mon, MMR at 6 and 12 mon, and MR4 at 6,12, and 18 mon. Moreover, the 2nd line 2nd generation TKI group recovered from their intolerance and resistance to 1st generation TKIs and had almost equivalent rates at CCyR at 12 and 18 mon, and MMR at 3 and 18 mon. Thus, 2nd line TKIs may be a reasonable option for the purpose of producing an early response and as an alternative treatment option for CML patients not suitable for treatment with 1st generation TKIs.

In the 2nd instance, the control of adverse effects associated with TKI therapy may be the single most important strategy to maintain adherence to TKI treatment. The adherence to TKI treatment may also impact the treatment response and treatment outcome of CML.[5,17] In our study, all grades of adverse effects by TKIs represented approximately 60% of cases, a finding which is consistent with previous reports.[5,8-10] Approximately 50% of the CML patients in this study developed grade 1-2 adverse effects, which is consistent with the results published by Kumamoto *et al*., who showed that the reduction of TKI dosage may be based on height, body weight, and BSA in Japan,[18] and that grade 1-2 adverse effects were controlled by TKI dose reduction and switch to another TKI. These methods may be useful in maintaining adherence to TKI in CML patients. For unmanageable adverse effects of TKI (grade 3), low-dose TKI treatment in a dose-escalation manner may be a useful tool to control adverse effects and CML status.[19] Thus, controlling adverse effects, ensuring optimal TKI treatment duration, and maintaining adherence to TKI therapy may be crucial for achieving long-term remission of CML.

In the third instance, prevention of resistance to TKI, including BC, is crucial for increasing the treatment response rate and treatment outcomes of CML patients. In our study, 21.6% (10/51) of CML patients showed resistance to 1st generation TKIs, but did not have mutation of the *BCR-ABL* gene. In such cases, changing to 2nd generation TKIs may be effective in controlling CML. Moreover, in our study, 2 CML patients in CCyR following treatment with a 1st generation TKI developed sudden BC within 1-2 mon, which was consistent with previous reports.[20,21] Thus, the careful monitoring and control of disease progression in CML patients are extremely important.[20,21] The condition of the latter 2 patients was improved by dose-escalated 1st generation TKI plus HSCT or 2nd generation TKI plus HSCT. Therefore, the role of HSCT in CML treatment remains vital for preventing disease progression and BC, consistent with the 2015 NCCN guidelines.[22]

Finally, social factors influencing CML treatment, such as economic issues (particularly in the elderly), and pregnancy (particularly in young patients), are important to consider.[23,24] The effect that these social factors have on CML therapy may be difficult to resolve. In terms of elderly patients, a

discussion may be required as to ways in which to support the elderly financially. In terms of pregnant CML patients, there is very limited clinical data regarding the side effects of TKI for pregnancy.[24] Thus, further study of TKI is essential for clarifying the potential side effects of TKI in pregnant mothers and infants.

In conclusion, our study demonstrated that 1st and 2nd generation TKI therapy of CML patients led to high treatment response and treatment outcome rates. However, sudden BC during TKI and social issues, including economic problems and pregnancy, are serious concerns for TKI treatment in CML patients. In the future, further deep molecular response to TKI treatment is required to achieve a cure for CML.

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CONFLICT OF INTEREST

The authors state that they have no Conflicts of Interest (COI).

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