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【 ORIGINAL ARTICLE 】

Efficacy and Cardiovascular Adverse Events of Long-term Treatment with Tyrosine Kinase Inhibitors for Chronic Myeloid Leukemia: A Report from the Nagasaki CML Study Group

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Abstract:

Objective The standard treatment for chronic myeloid leukemia (CML) is the continuous use of tyrosine kinase inhibitors (TKIs), which results in a favorable prognosis for the majority of patients. Recent studies have identified cardiovascular diseases (CVDs) as late adverse events (AEs) related to TKIs. In this study, we evaluated the long-term efficacy and AEs of TKIs, focusing on CVDs.

Methods We performed a retrospective survey of CML patients (diagnosed from 2001 to 2016) treated with TKIs in Nagasaki Prefecture. Clinical data were obtained from their medical records. We analyzed the survival, estimated cumulative incidence of CVDs, and risk factors for CVD among CML patients treated with TKIs.

Results The overall survival rate of 264 CML patients treated with TKIs (median age 58 years old) was 89.6% [95% confidence interval (CI), 84.9-92.9%], and 80.5% (95% CI, 73.4-85.9%) at 5 and 10 years after the CML diagnosis, respectively. CVD events occurred in 26 patients (9.8%, median age 67.5 years old) with a median 65.5 months of TKI treatment. The cumulative incidences at 2 and 5 years was 2.4% (95% CI, 1.0-4.8%) and 5.2% (95% CI, 2.8-8.6%), respectively. Hypertension and a high SCORE chart risk at the diagnosis of CML were associated with CVD events during TKI treatment.

Conclusion TKI treatment contributed to the long-term survival of CML patients in Nagasaki Prefecture in a "real-world" setting, but the incidence of CVDs seemed to be increased in these patients. A proper approach to managing risk factors for CVD is warranted to reduce CVD events during TKI treatment.

Key words: chronic myeloid leukemia, tyrosine kinase inhibitor, cardiovascular disease, adverse event

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Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by the presence of the *BCR-ABL1* fusion gene. CML in the chronic phase (CP) is now treated with tyrosine kinase inhibitors (TKIs) targeting the BCR-ABL1 fusion protein as a standard of care, which has resulted in a long-term survival for CML patients (1, 2).

Recent advances in CML management have made it possible to discontinue TKI treatment for a select group of patients after certain periods of a very good response to TKI treatment (3-5). However, patients need to continue TKI treatment for at least several years before discontinuation, and lifelong treatment is probably necessary for the majority of patients. This situation has prompted analyses of the long-term efficacy and adverse events (AEs) of TKIs as well as other diseases that develop during long treatment periods.

Several studies, including one in Japanese patients, have highlighted the increased risk of cardiovascular diseases (CVDs) among CML patients receiving TKI treatment (6-8). Recent reports pointed out the positive relationship between the increased incidence of CVDs and the type, dose, and duration of TKI treatment (9). Considering the potential impact of CVDs on the patient survival and quality of life, it is very important to investigate the current situation in CML management.

We have been studying CML patients in Nagasaki Prefecture since the introduction of TKIs in clinical practice and reported the molecular response of CML to TKIs by measuring the *BCR-ABL1* fusion transcripts, changes in the long-term survival (10), relationship between the response to TKI treatment and its blood concentration (11), and the mechanism underlying resistance against TKIs (12). The survival of CML patients in Nagasaki has improved drastically since the introduction of TKI treatment, overcoming the difference in patients' backgrounds between the clinical trial and the "real-world" setting. However, physicians treat many patients with a poor organ function and comorbidities, which often match the exclusion criteria of clinical trials, so these patients have a high risk of AEs.

In this study, we analyzed the current situation of CML patients receiving TKI treatment in clinical practice and the AEs of long-term TKI treatment, particularly CVDs.

Materials and Methods

Patients

We conducted a retrospective survey of patients with CML, 16 years or older who were treated or newly diagnosed between November 2001 and September 2016 at 11 institutions in Nagasaki Prefecture (listed in the acknowledgment). There were 272 patients with CML who were positive for Philadelphia chromosome and/or the *BCR-ABL1* fusion gene. Among these 272 patients, 8 did not receive TKI treatment: 2 patients received allogeneic stem cell transplantation (allo-SCT) as an initial therapy, and 2 were treated with interferon, 3 with cytotoxic agents, and 1 with supportive care only. Thus, 264 CML patients were ultimately analyzed for the development of CVD events (see "Diagnosis of diseases" in detail) during TKI treatment.

Data were updated as of March 2017. Clinical data for each patient, such as the diagnosis, treatment, accompanying diseases, occurrence of CVD events, prognosis, etc., were collected from the medical records of the hospitals. This study was approved by the Institutional Review Board or Ethics Committee of each participating institute.

The diagnosis of diseases

The clinical phase of the CML was classified using the criteria of the World Health Organization (WHO) classification (13), and the initial response to TKIs was evaluated following the Practical Guidelines for Hematological Malignancies published by the Japanese Society of Hematology (14). A major molecular response (MMR) was defined as International Scale (IS) of *BCR-ABL1* transcript at ≤0.01% (3-log reduction or less from the initial amount) or <50 copies/μg RNA using the Amp-CML method. CML-related death was defined as any death during the accelerated phase (AP) or blast crisis (BC) of CML. CVD was defined as any ischemic heart disease (IHD), such as acute myocardial infarction and angina pectoris, ischemic cerebrovascular disease (ICD) (including cerebral infarction, cardiogenic embolism, and lacunar infarction), and peripheral arterial occlusive disease (PAOD). The risk of cardiovascular disease was assessed using the SCORE chart (15).

Statistical analyses

Descriptive statistics were used to summarize the variables related to the patient demographics and the kinds of TKIs. Categorical variables were compared between groups using Fisher's exact test. Continuous variables were compared using the Mann-Whitney U test. Cumulative incidence curves were used in a competing-risk setting to calculate the probabilities of developing CVDs and malignancies. Regarding the incidence of CVD events, death without the development of CVD events and allo-SCT were the competing events. To evaluate the influence of the CVD event during TKI treatment on the survival, proportional hazard modeling was performed, treating the CVD as a time-dependent covariate.

Statistical analyses and graphical presentations were performed using the EZR software program, version 1.24 (Saitama Medical Center, Jichi Medical University) (16), and the Statistical Analysis Software program (SAS version 9.4 for Windows; SAS Institute, Cary, USA).

Results

Clinical characteristics and general situation of all patients

Most of the CML patients in Nagasaki Prefecture had been diagnosed and treated in the 11 institutions participating in this study (10). In total, 223 patients (84.5%) were diagnosed between November 2001 and September 2016, and 41 (15.5%) were diagnosed before this period. On average, 15.5 cases of CML were newly diagnosed each year in this study group. Of note, Nagasaki Prefecture has a population of about 1.4 million.

The clinical characteristics at the CML diagnosis of the 264 patients who received TKI treatment are shown in Table 1. There was a slight male predominance (146 men, 55.3%) as we previously reported (12), with a median age at the diagnosis of 58 years old (range, 17-89 years old). In terms of the clinical phase of the CML at the diagnosis, 238 patients had CML in CP (90.2%), 19 in AP (7.2%), and 7 in BC (2.6%). Fifty-two patients had a smoking history. Regarding their medical history, 23 (8.7%) and 35 (13.2%) patients had CVDs and malignancies before the diagnosis of CML, respectively. The initial TKI treatment was imatinib for 170 patients (64.4%), nilotinib for 41 (15.5%), dasatinib for 52 (19.7%), and bosutinib for 1 (0.4%). Among the 264 patients, 79 (29.9%) were administered ≥2 types of TKIs during the study period. The first and second TKIs are shown in Table 2. Twenty patients received a third-line TKI. The reasons for the change from the first to second-line TKI were intolerance (28 patients, 35.4%), an insufficient response (25, 31.6%), other reasons (7, 8.9%), and unknown reasons (19, 24.1%). Five patients (1.9%) received allo-SCT; TKI treatment was administered after transplantation in 4 of these patients and before transplantation in the other 1 patient.

The overall survival (OS) of all patients at 5 and 10 years after the diagnosis of CML was 89.6% [95% confidence interval (CI), 84.9-92.9%] and 80.5% (95% CI, 73.4-85.9%), respectively, with a median follow-up period of 6.5 years (Fig. 1). During this study period, 56 patients died. The most frequent cause of death was the progression of CML with a disease status of BC (n=16, 28.6%), followed by infection (n=15, 26.8%), and malignancies other than CML (n =10, 17.9%) (Table 3). CVD-related death was reported in 4 patients (7.1%) which related to cardiac and cerebral damage-relating diseases. The median age of the deceased patients was 78 years old (range, 35-97 years old), and they had a median 5.6 years of TKI treatment after the CML diagnosis. Because the survival curve started to decline sharply around 10 years from the time of the diagnosis (Fig. 1), we checked the cause of death among them. Twenty-four patients with a median age of 83 years old (range, 51-97 years old) died ≥9 years after the CML diagnosis. The major causes of death in these patients were infection (n=7), CML progression (n=5), malignancy other than CML (n=5), and senility (n=2). Heart failure, renal failure, and acute subdural hematoma were the causes of death in one patient each. Information was not obtained for two patients.

Patients who experienced CVD events during TKI treatment

After starting TKI treatment, 26 patients (9.8%) experienced new CVD events (CVD group, Table 1). Detailed data of the individual patients in the CVD group are shown in Table 4, and the time course of TKI treatment for these patients is shown in Fig. 2. The median patient age at the onset of the first CVD event during TKI treatment in these patients was 77 years old (range, 53-89 years old), and the man/woman ratio in these patients was 1.9 (Table 4). Seven patients had been diagnosed with neoplasms other than CML before they experienced CVD events. The most frequent CVD was ICD (n=12, 46.2%), followed by IHD (n= 10, 38.5%) and PAOD (n=4, 15.3%) (Table 4). In terms of the response to TKI treatment, the percentages of major molecular response were 77.3% (17 out of 22 patients) in the CVD patients and 84.7% (188 out of 222 patients) in the non-CVD patients, respectively, without a significant difference (p=0.177). Among the 26 patients in the CVD group, 10 were administered ≥2 TKIs before CVD events, as shown in Fig. 2. The types of TKI being taken at the CVD events were imatinib (IMA, 7 patients), dasatinib (DAS, 2 patients), nilotinib (NIL, 16 patients), and no TKI treatment (1 patient); however, the impact of each TKI on the CVD was difficult to evaluate due to the varied combinations and treatment durations of TKIs.

The median time from the start of TKI treatment to the first CVD event was 67.2 months (range, 0.2-173.7 months), and the cumulative incidences of CVDs at 2 and 5 years after starting TKI treatment were 2.4% (95% CI, 1.0-4.8%) and 5.2% (95% CI, 2.8-8.6%), respectively (Fig. 3). One of the 26 patients died of CVD within a month after the onset of the event. TKI treatment was stopped in two patients and interrupted and then restarted in one patient after CVD. In total, 8 of the 26 patients died during the study period, and as previously mentioned, 1 death seemed directly related to the CVD event. An additional three patients died within six months of the CVD events, and their causes of death, such as infection and pneumonia, were judged to be related to disability after CVDs. Six of the 8 patients who died were over 80 years old, and 4 died of pneumonia and/or heart failure. None of the 26 patients experienced clinical progression of the CML.

The 5- and 10-year OS rates were 87.7% (95% CI, 66.4-95.8%) and 73.3% (95% CI, 45.0-88.6%), respectively, for those in the CVD group and 89.9% (95% CI, 84.8-93.3%) and 81.5% (95% CI, 74.1-86.9%), respectively, for those who did not experience CVD events (non-CVD group). To assess the impact of CVD during TKI treatment on the survival of CML patients, the clinical factors at the diagnosis

Table 1. Clinical Characteristics of the Patients at the Diagnosis of Chronic Myeloid Leukemia (CML).

	All n=264	Patients with cardiovascular disease (CVD group) n=26	Patients without CVD (non-CVD group) n=238	p value (CVD vs. non-CVD group)
Sex, n (%)				
male	146 (55.3)	17 (65.4)	129 (54.2)	0.271
female	118 (44.7)	9 (34.6)	109 (45.8)	
Age, median (range)	58 (17-89)	67.5 (50-81)	56 (17-89)	0.006
CML phase at diagnosis, n (%)				
Chronic phase	238 (90.2)	25 (96.2)	213 (89.5)	0.429
Accelerated phase	19 (7.2)	1 (3.8)	18 (7.6)	
Blast crisis	7 (2.6)	0	7 (2.9)	
Sokal score, n (%)				
Low	91(34.5)	6 (23.1)	85 (35.7)	0.556
Int	107 (40.5)	13 (50.0)	94 (39.5)	
High	55 (20.8)	6 (23.1)	49 (20.6)	
Uncertain	11 (4.2)	1 (3.8)	10 (4.2)	
Performance status, n (%)				
0-1	244 (92.4)	25 (96.2)	219 (92.0)	1
2-4	8 (3.0)	0	8 (3.4)	
unknown	12 (4.6)	1 (3.8)	11 (4.6)	
Allogenic hematopoietic stem cell transplantation at any time, n (%)				
Yes	5 (1.9)	0	5 (2.1)	1
No	259 (98.1)	26 (100)	233 (97.9)	
Period of diagnosis of CML, n (%)				
Before November 2001	41 (15.5)	6 (23.1)	35 (14.7)	0.287
After November 2001	223 (84.5)	20 (76.9)	203 (85.3)	
TKI therapy (First line), n (%)				
Imatinib	170 (64.4)	18 (69.2)	152 (63.9)	0.004
Nilotinib	41 (15.5)	8 (31.8)	33 (13.9)	
Dasatinib	52 (19.7)	0	52 (21.8)	
Bosutinib	1 (0.4)	0	1 (0.4)	
Glucose intolerance, n (%)				
Yes	25 (9.5)	4 (15.4)	21 (8.8)	0.257
No	167 (63.3)	14 (53.8)	153 (64.3)	
Uncertain	72 (27.2)	8 (30.8)	64 (26.9)	
Hypertension, n (%)				
Yes	94 (35.6)	17 (65.4)	77 (32.4)	0.001
No	137 (51.9)	6 (23.1)	131 (55.0)	
Uncertain	33 (12.5)	3 (11.5)	30 (12.6)	
Hyperlipidemia, n (%)				
Yes	91 (34.5)	7 (28.0)	84 (35.3)	0.38
No	39 (14.8)	5 (20.0)	34 (14.3)	
Uncertain	134 (50.7)	14 (52.0)	120 (50.4)	
History of CVD, n (%)				
Yes	23 (8.7)	5 (19.2)	18 (7.6)	0.052
No	235 (89.0)	21 (80.8)	214 (89.9)	
Uncertain	6 (2.3)	0	6 (2.5)	
History of malignancy, n (%)				
Yes	35 (13.2)	5 (19.2)	30 (12.6)	0.395
No	223 (84.5)	21 (80.8)	202 (84.9)	
Uncertain	6 (2.3)	0	6 (2.5)	
History of smoking†, n (%)				
Yes	52 (19.7)	6 (23.1)	46 (19.3)	0.617
No	196 (74.2)	18 (69.2)	178 (74.8)	
Uncertain	16 (6.1)	2 (7.7)	14 (5.9)	
BMI (kg/m^2), n (%)				
BMI ≥30	9 (3.4)	1 (3.8)	8 (3.4)	0.93
BMI <30	245 (92. 8)	25 (96.2)	220 (92.4)	
Uncertain	10 (3.8)	0	10 (4.2)	
eGFR (mL/min/1.73 m^2), n (%)				
≥60	184 (69.7)	17 (65.4)	167 (70.2)	0.616
≤59	61 (23.1)	7 (26.9)	54 (22.6)	
Uncertain	19 (7.2)	2 (7.7)	17 (7.2)	

Five cases overlapped in patients with CVD and with malignancy.

† History of smoking was defined as former and current smoking.

CML: chronic myeloid leukemia, CVD: cardiovascular disease, TKI: tyrosine kinase inhibitor, BMI: body mass index, eGFR: estimated glomerular filtration rate

Table 2. Number of Patients Treated with First, and Second-line TKIs.

			2nd line TKI			
		no change	Imatinib	Nilotnib	Dasatinib	Bostinib
1st line TKI (number of patients)	Imatinib (170)	109	-	36	25	0
	Nilotnib (41)	31	4	-	5	1
	Dasatinib (52)	44	3	5	-	0
	Bostinib (1)	1	0	0	0	-

TKI: tyrosine kinase inhibitor

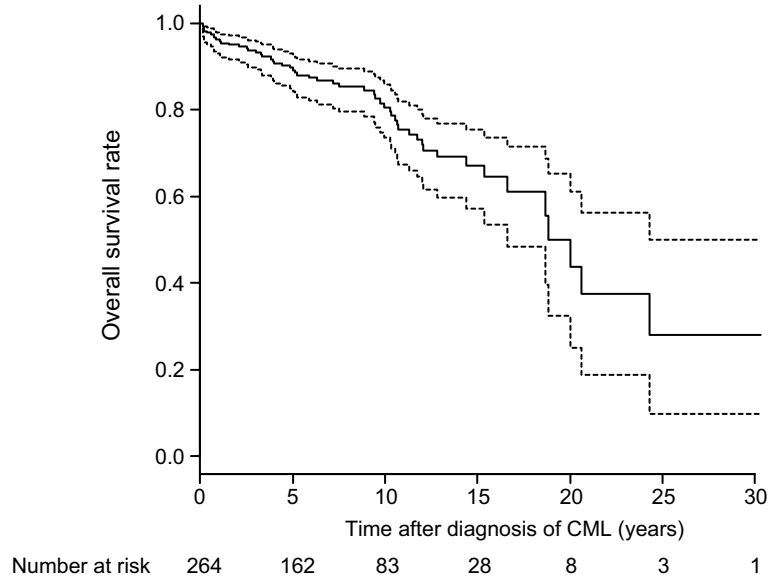

Figure 1. The overall survival curve of all chronic myeloid leukemia (CML) patients (black line) with 95% confidence interval (broken lines).

and the CVD event were analyzed using proportional hazard modeling, and the age at the diagnosis and clinical phase of CML were found to be significantly related, whereas CVD events were not (Table 5). All patients but 1 with a low platelet count received antiplatelet (19 patients) or anticoagulant therapy (5 patients) after the first CVD event (the patient that died within 1 month after CVD was excluded). However, six patients experienced additional CVD events, including two with multiple recurrences under TKI treatment. The same TKI was continuously used after the first CVD event for 21 of the patients.

Clinical factors related to the development of CVD

To determine the clinical factors predictive of the development of CVD under TKI treatment, we compared the clinical features at the CML diagnosis between patients in the CVD and non-CVD groups (Table 1), focusing on generally reported risk factors for CVD, such as diabetes mellitus (glucose intolerance), hyperlipidemia, hypertension, obesity [elevated body mass index (BMI)], and smoking habits. There was a statistically significant difference in the frequency of hypertension between the 2 groups (65.4% in the CVD group vs. 32.4% in the non-CVD group, p=0.001). The difference in the frequency of a history of CVD between the 2 groups showed marginal significance (21.0% in the CVD group vs. 7.6% in the non-CVD groups, p=0.052). However, the frequencies of glucose intolerance, hyperlipidemia, BMI ≥30 kg/m^2, and smoking habit were similar between the 2 groups. The percentage of patients with hypertension in the CVD group increased from 65.4% at the CML diagnosis (Table 1) to 73.1% at the onset of CVD. The CVD group was significantly older than the non-CVD group at the diagnosis of CML (median age 67.5 vs 56 years old, respectively, p=0.006; Table 1).

We also tested whether or not the currently available risk assessment system for CVD, the SCORE chart (15), provided valuable information for CVD among CML patients with TKI treatment. SCORE chart data were sufficient in 13 out of 26 patients in the CVD group and in 136 out of 236 in the non-CVD group. The distribution of patients in risk categories of the SCORE chart was significantly different between the 2 groups (p=0.005), with no patients with a low risk included in the CVD group. It was suggested that patients in the CVD group had a higher baseline risk than those in the non-CVD group at the diagnosis of CML (Table 6).

Table 3. Causes of Death.

Total deaths, n	56
Median age at the time of death, y (range)	78 (35-97)
Median age at the diagnosis of CML, y (range)	71 (23-88)
Male / female, n	32 / 24
Median time from diagnosis of CML to death, y (range)	5.6 (0.2-29.8)
Cause of death, n (%)	
CML-related death	16 (28.6)
Infection	15 (26.8)
Pneumonia	11
Acute cholangitis	2
Sepsis	1
Other	1
Malignancy	10 (17.9)
Colon cancer	1
Gastric cancer	2
Lung cancer	3
Malignant lymphoma	2
Pancreatic cancer	2
Heart failure	2 (3.6)
Senility	2 (3.6)
Sudden death	2 (3.6)
Other	5 (8.9)
Acute myocardial infarction	1
Acute subdural hematoma	1
Cerebral hemorrhage	1
Cirrhosis	1
Renal failure	1
Uncertain	4 (7.1)
CVD related death	4 (7.1)
Acute myocardial infarction	1
Heart failure after acute myocardial infarction	1
Pneumonia after cerebral infarction	2

CML: chronic myeloid leukemia, CVD: cardiovascular disease

Discussion

In the present study, we analyzed the data of CML patients treated with TKIs in Nagasaki Prefecture in daily practice and confirmed their long-term survival, with a 10-year OS rate of 80.5%, even including patients with CML in AP (7.2%) and BC (2.6%) at the diagnosis. These data demonstrated an excellent long-term efficacy of TKIs for CML.

Physicians treat a wider variety of patients, such as older patients, in the real-world than are seen among patients treated in clinical trials. For example, the median age was 50 years old in the IRIS study, an imatinib trial (17), and 58 years old in this study; however, the long-term survival of our study patients was similar to that among the patients in the IRIS trial and its follow-up study [10-year OS rate of 83.3% in the IRIS study (18)] as well as in the long-term observation of second-generation TKI studies (19, 20). We also found that the cumulative incidence of CVD events among CML patients receiving TKI treatment was 2.4% and 5.2% at 2 and 5 years, respectively, which seemed slightly higher than those values reported by another Japanese group (8). Many groups have reported increased incidences of CVDs among patients treated with TKIs, and although we were unable to directly compare the incidence rate of CVD between CML patients and the general population, it seemed that vascular AEs related to TKIs were also increased in this study population in Nagasaki. The incidence of IHD in our study was 5.8 per 1,000 person-years (without adjustment for age or sex), and that reported by Fujioka et al (8). was 5.68 (with adjustment for age and sex), which supports our speculation.

When we compared the clinical factors at the diagnosis of CML between the CVD and non-CVD groups, we found that hypertension at the diagnosis of CML was significantly more frequent in the CVD group than in the non-CVD group, but other common risk factors for CVDs, such as glucose intolerance, hyperlipidemia, an elevated BMI, and a smoking habit, were not. Several study groups have reported an influence of these factors (7-9), and the difference in CVD-related factors might be due to differences in the background characteristics of the study populations; most other studies analyzed data from clinical trials, whereas we studied real-world patients, including patients with different

Table 4. Indivieula Data of Patients in CVD Group.

UPN	Sex	Age at CVD	Type of CVD	Diagnosis of CVD	Time from TKI Treatment to CVD (month)	Achievemnt of MMR at CVD	Type of TKI at CVD	Hyper-tension	Glucose intoler-ance	Hyperlip-idemia	Smoking	SCORE	Preventive medicine for CVD	
													before CVD	after first CVD
UPN-01	Male	77	IHD	AMI	3	No	IMA	Yes	No	Unknown	No	Moderate	No	Yes
UPN-02	Female	68	IHD	AMI	87	Yes	NIL	Yes	No	Unknown	No	Moderate	No	Yes
UPN-03	Male	85	ICD	Cerebral infarction	163	Yes	IMA	No	Unknown	Unknown	No	n.a.	No	Yes
UPN-04	Female	83	ICD	Cardiogenic embolism	118	No	NIL	Yes	No	Unknown	No	n.a.	No	Yes
UPN-05	Male	59	IHD	Angina pectoris	26	Yes	NIL	Yes	Unknown	Unknown	Yes	n.a.	No	Yes
UPN-06	Female	89	IHD	AMI	161	Yes	IMA	Yes	No	Yes	No	Moderate	No	Yes
UPN-07	Male	78	ICD	Cardiogenic embolism	101	Yes	NIL	Unknown	Unknown	Unknown	Unknown	n.a.	No	No
UPN-08	Male	71	PAOD	ASO	30	Yes	NIL	Yes	No	No	Yes	Verry high	No	Yes
UPN-09	Female	67	IHD	AMI	41	Yes	NIL	Yes	No	Unknown	No	n.a.	Yes	Yes
UPN-10	Male	54	IHD	ACS	52	Unknown*	NIL	No	No	Yes	No	n.a.	No	Yes
UPN-11	Male	69	IHD	AMI	83	No	DAS	No	Unknown	Yes	Yes	Moderate	No	Yes
UPN-12	Male	82	ICD	Lacunar infarction	15	No	IMA	Yes	No	Yes	Yes	High	Yes	Yes
UPN-13	Male	77	ICD	Atherothrombotic cerebral infarction	157	Yes	NIL	Yes	Unknown	Yes	No	Moderate	Yes	Yes
UPN-14	Male	83	IHD	AMI	21	Yes	NIL	Yes	Unknown	Unknown	No	n.a.	No	Yes
UPN-15	Male	60	IHD	Angina pectoris	40	Yes	NIL	Unknown	Yes	No	No	n.a.	No	Yes
UPN-16	Male	79	ICD	Cardiogenic embolism	0	Unevaluable**	NIL	Yes	Unknown	No	No	n.a.	Yes	Yes
UPN-17	Female	81	ICD	Lacunar infarction	76	Unknown	DAS	No	No	Unknown	No	Moderate	No	Yes
UPN-18	Male	72	ICD	Lacunar infarction	135	Yes	NIL	No	No	Yes	No	n.a.	No	Yes
UPN-19	Male	80	ICD	Atherothrombotic cerebral infarction	69	Yes	NIL	Yes	No	Unknown	No	n.a.	No	Yes
UPN-20	Male	54	PAOD	Carotid artery stenosis	12	Yes	NIL	Yes	No	Yes	Yes	Moderate	Yes	Yes
UPN-21	Male	73	IHD	AMI	101	Yes	IMA	Yes	Yes	Unknown	Unknown	n.a.	No	Yes
UPN-22	Female	82	PAOD	ASO	94	Unknown	IMA	Yes	No	No	No	High	No	Yes
UPN-23	Female	70	ICD	Cardiogenic embolism	1	Unevaluable	NIL	Yes	Yes	No	No	Moderate	Yes	Yes
UPN-24	Male	53	PAOD	ASO	24	Yes	NIL	No	Yes	Unknown	Yes	Moderate	No	Yes
UPN-25	Female	78	ICD	Cardiogenic embolism	62	No	IMA	Yes	No	Unknown	No	Moderate	No	Yes
UPN-26	Male	87	ICD	Atherothrombotic cerebral infarction	174	Yes	None	Unknown	Yes	Unknown	No	n.a.	No	Yes

*, no molecular evaluation for one year before CVD; **, short duration of TKI treatment.

CVD: cardiovascular disease, TKI: tyrosine kinase inhibitor, IHD: ischemic heart diseasen, ICD: ischemic cerebrovascular disease, PAOD: peripheral arterial obstructive disease, AMI: acute myocardial infarction, ASO: arteriosclerosis obliterance, ACS: acute coronary syndrome, n.a.: not availavle

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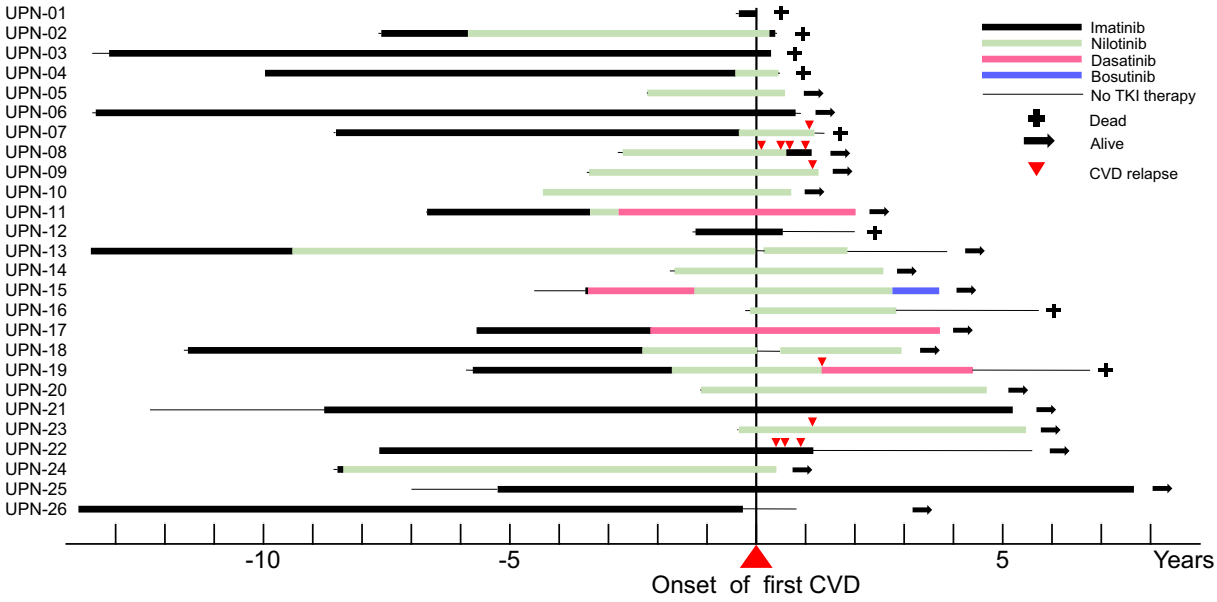

Figure 2. **The time course of TKI treatment and CVD events for each patient in the CVD group. Each line represents the clinical course of TKI treatment for each patient. Black line, imatinib; green line, nilotinib; red line, dasatinib; blue line, bostinib. The thin line indicates those with no TKI treatment. Inverted red triangle, CVD event; +, dead; →, alive. TKI: tyrosine kinase inhibitor, CVD: cardiovascular disease**

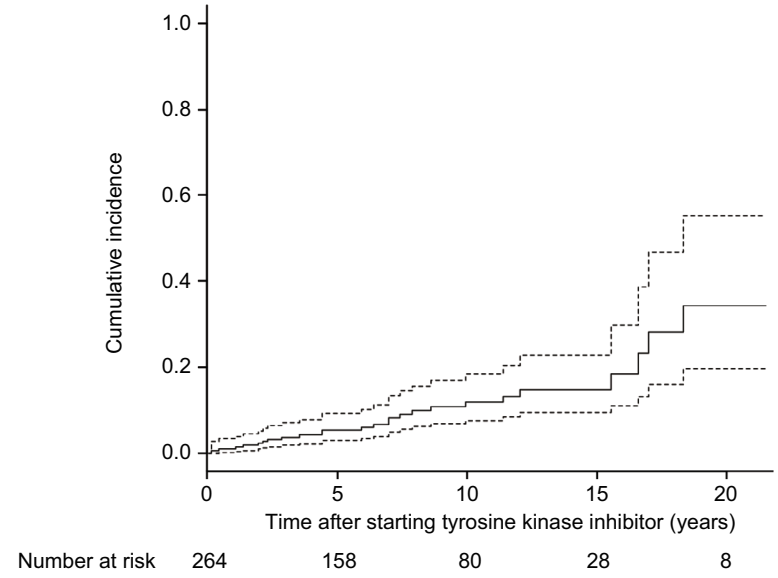

Figure 3. **Cumulative incidence curve of cardiovascular disease (black line) with 95% confidence interval (broken lines).**

Table 5. **Multivariate Analysis for Survival of CML Patients.**

Factors	Hazard ratio	95% CI	p value
CVD event (absent vs. present)	0.885	0.357-2.196	0.793
Sex (male vs. female)	1.963	1.012-3.809	0.046
Age at diagnosis	1.069	1.039-1.100	<0.001
PS at diagnosis	0.988	0.642-1.520	0.957
Clinical phase of CML (blastic, accelerate, chronic)	3.573	1.932-6.606	<0.001
Sokal risk (high, int, low)	1.239	0.760-2.018	0.39

CML: chronic myeloid leukemia, CVD: cardiovascular disease, CI: confidence interval, PS: performance status

Table 6. Number of Patients in Risk Categories by SCORE Chart.

Rsik category by the SCORE chart	non-CVD group (%)	CVD group (%)	p=0.005
Low	51 (37.5)	0	
Moderate	76 (55.9)	10 (76.9)	
High	6 (4.4)	2 (15.4)	
Verry high	3 (2.2)	1 (7.7)	
Total	136	13	

CVD: cardiovascular disease

stages of CML and multiple comorbidities. Although sufficient data for several patients were available (13 patients in CVD and 136 in non-CVD group), the distribution in the SCORE chart risk category differed between the 2 groups at the diagnosis of CML, supporting the importance of the background characteristics of patients on the CVD risk during TKI treatment. These findings suggest that the management of these factors is important for reducing CVD during TKI treatment. There are five types of TKIs available for CML treatment in Japan, and the TKI type has also been reported to be related to the incidence of CVD events (9, 21). However, because many patients received two or more types of TKIs during the treatment period, mostly because of TKI AEs or intolerance, we were unable to evaluate the risk of each TKI or the impact of the total TKI dose on the incidence of CVD events.

CVD was a direct cause of death in one patient, and three additional patients died within six months of the CVD events, suggesting a strong influence of CVDs on the clinical course of the patients. We found that six patients experienced CVD recurrence despite antiplatelet or anticoagulant treatment. Considering the long-term survival of CML patients and the impact of CVD events on the patients' lives, it is necessary to develop a new strategy for the prevention and treatment of CVDs. Because hypertension was significantly related to CVD in this study, its strict control would be one way of achieving this.

Recent studies have demonstrated the possibility of TKI cessation in patients who have maintained a deep molecular response for certain periods of time. Intensive treatment with a TKI followed by TKI discontinuation may be a viable future strategy for treating CML (22). Considering the impact of CVD on not only the survival but also the quality of life, a quick introduction into a deep molecular response followed by the cessation of the TKI may help maintain the efficacy of the TKI while at the same time reducing TKI-related CVD in CML patients.

As a long-term survival is expected for most patients, real-world data will continue to be important for evaluating the benefit and AEs associated with standard and new treatments for CML, including emerging strategies for the discontinuation of TKIs.

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