Annals of Hematology (2018) 97:2081–2088
https://doi.org/10.1007/s00277-018-3412-8

ORIGINAL ARTICLE

Features of vascular adverse events in Japanese patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors: a retrospective study of the CML Cooperative Study Group database

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Received: 25 February 2018 / Accepted: 20 June 2018 / Published online: 26 June 2018

Abstract

This study investigated the incidence rate and features of vascular adverse events (VAEs) in Japanese patients with chronic myeloid leukemia (CML) who were treated with tyrosine kinase inhibitors (TKIs). The analysis included 369 CML patients in the chronic or accelerated phases, selected from the CML Cooperative Study Group database; 25 events in 23 (6.2%) of these patients were VAEs. At the time of VAE incidence, nine patients were on treatment with imatinib, 12 with nilotinib, three with dasatinib, and one with bosutinib. VAE incidence comprised 13 cases of ischemic heart disease (IHD), eight of cerebral infarction (CI), and four of peripheral arterial occlusive disease (PAOD). IHD incidence rate in the study population was higher than that in the age-matched general population, particularly in nilotinib-treated patients, while CI incidence rate was almost equivalent. Compared with the Suita score, the SCORE chart and the Framingham score risk assessment tools detected more patients with high or very high risk of VAEs. In conclusion, incidence of IHD requires closer monitoring in nilotinib-treated patients. More detailed investigations for determining the most useful tool to predict VAE incidence and long-term analysis of therapy-related VAE cases are needed for improving safety during TKI therapy.

Keywords Cardiovascular disease · Tyrosine kinase inhibitor · Chronic myeloid leukemia · Vascular adverse events · Japanese patients

Introduction

Chronic myeloid leukemia (CML) is a disease of hematopoietic stem cells, resulting from oncogenic translocation between chromosomes 9 and 22 that leads to the formation of the *BCR–ABL1* fusion gene. Treatment of the chronic phase (CP)-CML has dramatically changed since the emergence of the first-in-class tyrosine kinase inhibitor (TKI) imatinib; and the TKI-based treatment has improved the outcomes of most CP-CML patients [1]. Currently, second-generation TKIs are available and have facilitated faster and deeper clinical responses as well as lower disease progression rates as opposed

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to imatinib [2–5]. On the other hand, longer treatment duration and the increase in number of available TKIs gave rise to various kinds of unexpected adverse events (AEs) [6]. In 2011, increased incidence of peripheral artery occlusive disease (PAOD) among nilotinib-treated patients was first reported [7], followed by incidences of VAEs including ischemic heart disease (IHD) and cerebral infarction (CI) [8]. Furthermore, it became clear from the results of several clinical trials that demonstrated increased incidence of VAEs owing to increases in TKI doses and treatment duration [2, 5]. Because of the reports of some patients dying, likely because of VAE incidence, these adverse events were considered as more fatal complications of TKI treatment [9, 10]. However, there are no available data concerning the clinical features of VAEs and the efficacy of currently available tools for assessing cardiovascular disease (CVD) risk in Japanese patients with CML. Here, we present the clinical entity of VAE incidence along with the estimation of the 1000 person-years risk during TKI treatment, including imatinib, nilotinib, and dasatinib, in patients with CML who were enrolled in the CML Cooperative Study Group. The risk of VAE incidence using three CVD risk assessment tools was also evaluated in patients who developed VAEs.

Methods

Patients

This study included patients who were diagnosed with CML, according to the European LeukemiaNet (ELN) criteria described previously [11], between April 2001 and January 2016. CML patients in the blastic phase (BP) and CML patients who used interferon-α or any chemotherapeutic agent prior to or in combination with TKI were excluded. However, the prior use of hydroxyurea was accepted in this analysis. The study was approved by the research ethics boards of each institution participating in the study and was conducted in accordance with the Declaration of Helsinki.

Statistical analysis

VAEs noted in the study patients included CI, IHD, and PAOD. All patients who developed VAEs were analyzed using three CVD risk assessment tools such as the SCORE chart [12], Framingham risk score (low, < 5 points; moderate, 5–10 points; and high, > 10 points) [13], and Suita score (low, < 41 points; intermediate, 41–55 points; and high, > 55 points) [14] to estimate the patients' 10-year risk of VAEs. Statistical analysis was performed using EZR software [15], which is a graphical user interface for the R programming language (The R Foundation for Statistical Computing Vienna, Austria; http://www.R-project.org/). VAE incidence rates (1000 person-years) were expressed as the number of patients with VAE divided by the total TKI treatment period. In brief, the incidence rates of IHD and CI were calculated using the data on age and gender (male/female) in Tables 2 and 3 of References #16 and #17, respectively, in each case [16, 17]. The incidence of IHD and CI event in this population was estimated from the summation of the incidence of each IHD and CI case, which was derived by multiplying the observation years by the incidence rate. The expected 1000 person-years was calculated by dividing the incidence by the total observation time. Comparison of IHD per 1000 person-years between Japanese general population and TKI-treated CML patients could show some differences because in this analysis, the 13 IHD events included one case of asymptomatic angina.

Results

Patient characteristics and TKI usage

The characteristics of the 369 patients along with their TKI usage are presented in Table 1. The median age of the study patients was 53.0 years (range 18–89); the total number of patients comprised 224 males and 145 females, and the median follow-up time was 71.8 months (range 1–196). At the start of the treatment, the median age and gender of the four TKI-treated groups were not significantly different (imatinib, 53.0

Table 1 Characteristics of patients enrolled in the study and treatments they received

Total number	369
Sex (male/female)	224/145
Age, median (range)	53.0 (18–89)
Disease stage	
Chronic phase	363
Accelerated phase	6
Total number of each TKI use	
Imatinib	197
Nilotinib	138
Dasatinib	140
Bosutinib	29
First-line therapy	
Imatinib	189
Nilotinib	81
Dasatinib	99
Sequential therapy	
Imatinib	10
Nilotinib	63
Dasatinib	49
Second-generation TKI only	
Nilotinib	70
Dasatinib	61

TKI tyrosine kinase inhibitor

[range 21–89] years; male, $n = 114$, female, $n = 85$; nilotinib, 52.5 [range 19–89] years, male, $n = 84$ and female, $n = 56$; dasatinib, 54.5 [range 18–89] years, male, $n = 91$ and female, $n = 52$; bosutinib, 56.0 [range 21–82] years, male, $n = 22$ and female, $n = 7$). At diagnosis, 363 patients were in the CP, and six in the accelerated phase. Twenty-five events of VAEs in 23 (6.2%) patients (two patients developed two VAEs each) were reported during the study period (Table 2). At the time of VAE incidence, nine cases were treated with imatinib, 12 with nilotinib, three with dasatinib, and one with bosutinib.

Details of VAEs and comparison of incidence rates between the Japanese general population and TKI-treated patients

Characteristics of patients who developed VAEs are listed in Table 2. Of the 25 VAEs observed, 13 were IHD, eight were CI, and four were PAOD (Fig. 1 and Table 2). Sixteen of the 23 patients with VAEs were men, and the median age was 61.0 years (range 35–85). The median treatment duration from the initiation of the current TKI was 78.7 months (range 0–139.7), and six nilotinib-treated patients were switched from other TKIs. With regard to treatment dose at the time of VAE incidence, nine patients were treated with nilotinib at a dose of 600 mg; one, 300 mg; and two, 150 mg; nine other patients were treated with 400-mg imatinib; three patients were treated with dasatinib at a dose of 100 mg; one patient was treated with 100-mg bosutinib. Of note, one out of the three dasatinib-treated patients developed acute myocardial infarction (AMI) on the day after dasatinib initiation; this patient had aortic valve stenosis, which was considered to be the trigger for AMI. The patient was treated with catheter-based coronary artery intervention and restarted on dasatinib at the same dose. No recurrence of IHD was observed.

To analyze the relationship between CVD and TKI, we calculated the incidence rate per 1000 person-years and then compared the VAE incidence rate in our study population with the age-matched general population (Table 3). The incidence rates of IHD, CI, and PAOD per 1000 person-years were 5.68, 3.50, and 1.75, respectively, among patients enrolled in the study. The incidence rates of IHD, CI, and PAOD per 1000 person-years, respectively, were 2.99, 2.25, and 1.50 during imatinib therapy; 15.09, 6.47, and 4.71 during nilotinib therapy; and 4.87, 2.43, and 0.00 during dasatinib therapy; however, in the age- and gender-matched Japanese general population, the adjusted incidence rates of IHD, CI, and PAOD per 1000 person-years were 1.787, 3.342, and not available, respectively.

Validation of the three CVD risk assessment tools

To evaluate the ability of the currently available three risk assessment tools about the prediction of VAE incidence, we evaluated the risk in patients who developed VAE. As shown in Table 2, according to the SCORE chart, three patients were assessed to have low risk; six, moderate risk; and 13, very high risk. According to the Framingham risk score, seven patients had low risk; eight, moderate risk; and seven, high risk; as per Suita score, eight had low risk; nine, intermediate; and four, high risk. Only four patients who developed VAE were assessed to be at high risk using the Suita score; most patients were assessed to be at very high and high risk of CVD using the SCORE chart ($n = 13$) and the Framingham risk scores ($n = 7$). The Suita, SCORE, and Framingham risk scores were not assessed for 2, 1, and 1 patient, respectively, due to missing data.

Cumulative incidence of VAEs during imatinib or nilotinib treatment

Cumulative incidence of VAEs during imatinib, nilotinib, or dasatinib treatments is shown in Fig. 2a (imatinib), Fig. 2b (nilotinib), and Fig. 2c (dasatinib). Median times of VAEs associated with each TKI are 95.1 (range 1–139.7), 29.3 (range 9.5–65.8), and 46.8 months (range 0–51.6), respectively. Of note, six out of ten patients in the nilotinib group received antecedent therapy with other TKIs for 19–124.5 months, while all patients classified into the imatinib group were treated with imatinib as first-line therapy.

Discussion

In this study, we investigated the clinical features and incidence rates of VAEs among Japanese patients with CML who received TKI treatment. The current study included 23 CML patients (25 events) from the CML Cooperative Study Group database who had developed VAEs. To our knowledge, this is the first report, based on the data obtained from clinical practice, regarding the incidence and clinical features of VAEs in Japanese patients with CML. We showed that the incidence rate of IHD was higher among all the CML patients who were treated with the three TKIs included in this study, particularly nilotinib-treated patients, compared with the Japanese general population. On the other hand, the incidence rate of CI was almost equivalent to that of the general Japanese population. These results suggest that the use of TKIs is a possible risk factor for IHD. However, the antecedent TKIs might have influenced the development of VAEs, because six out of ten patients who developed VAEs during nilotinib therapy had been pretreated with other TKIs (five, imatinib and one, dasatinib). The effect of antecedent therapy on the development of VAE should be investigated in the future. In accordance with our study results, a large-scale population-based study investigating VAE incidence in Sweden showed no increase in the incidence of CI during TKI therapy [18];

Table 2 Characteristics and treatments of patients with VAEs during TKI therapy

No.	Age	Sex	TKI	Dose (mg)	Duration (month)	1st Antecedent TKI	Dose (mg)	Duration (month)	Second antecedent TKI	Dose (mg)	Duration (month)	Total TKI duration (month)	Type of VAE	Framingham score	SCORE	Suita score
1	77	F	Dasatinib	100	0.0							0.0	IHD	Moderate	Very high	Intermediate
2	69	M	Imatinib	400	1.0							1.0	CI	High	Very high	High
3	85	F	Nilotinib	300	9.5							9.5	CI	High	Very high	Intermediate
4	82	M	Nilotinib	600	11.3							11.3	IHD	High	Very high	High
5	82	M	Bosutinib	100	9.6	Imatinib	300	0.5	Dasatinib	20	3.6	13.7	CI	High	Very high	High
6	69	M	Nilotinib	600	18.5	Imatinib	100	19.1				37.6	IHD	Moderate	Very high	Low
7	68	M	Imatinib	400	38.1							38.1	IHD	High	Very high	Intermediate
8	53	M	Nilotinib	600	38.6							38.6	PAOD	Moderate	Moderate	Low
9	67	M	Nilotinib	600	40.6							40.6	IHD	Moderate	Moderate	High
10	58	M	Dasatinib	100	49.9							49.9	IHD	Low	Very high	Intermediate
11	68	M	Dasatinib	100	51.6							51.6	CI	High	Very high	N/A
12–1	72	F	Nilotinib	150	18.0	Imatinib	400	56.2				74.3	IHD	Moderate	Very high	Intermediate
12–2	72	F	Nilotinib	600	31.0	Nilotinib	150	18.0	Imatinib	400	56.2	105.3	PAOD			
13	57	F	Imatinib	400	78.7							78.7	PAOD	Moderate	Very high	Low
14	35	F	Nilotinib	600	37.0	Dasatinib	100	46.8				83.8	CI	Low	Low	Low
15	51	M	Imatinib	400	103.7							103.7	IHD	Moderate	Moderate	Intermediate
16	66	M	Imatinib	400	103.7							103.7	PAOD	Low	Low	Intermediate
17	50	F	Nilotinib	600	38.4	Imatinib	400	68.0				106.4	IHD	High	Moderate	Low
18–1	39	M	Nilotinib	600	21.5	Imatinib	400	95.1				116.6	CI	Low	Low	Low
18–2	39	M	Nilotinib	150	22.0	Nilotinib	600	21.5	Imatinib	400	95.1	138.6	IHD			
19	51	M	Imatinib	400	133.0							133.0	CI	N/A	N/A	N/A
20	54	M	Imatinib	400	133.2							133.2	IHD	Low	Moderate	Low
21	61	M	Imatinib	400	134.0							134.0	IHD	Moderate	Very high	Intermediate
22	54	M	Imatinib	400	139.7							139.7	CI	Low	Moderate	Low
23	58	F	Nilotinib	600	65.8	Imatinib	400	124.5				190.3	IHD	Low	Very high	Intermediate

VAE vascular adverse event, *TKI* tyrosine kinase inhibitor, *F* female, *M* male, *IHD* ischemic heart disease, *CI* cerebral infarction, *PAOD* peripheral arterial occlusive disease, *N/A* not available

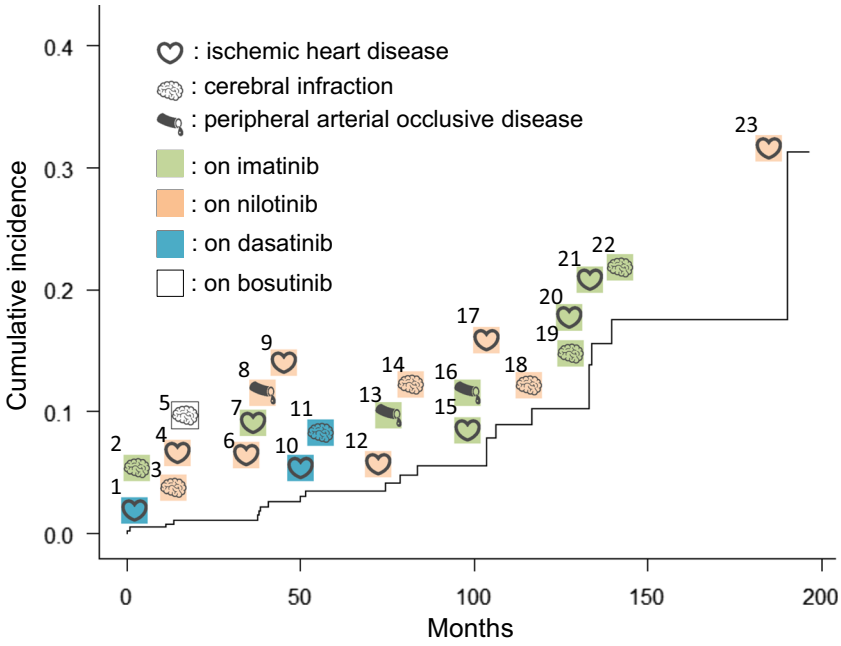

Fig. 1 Cumulative incidence of vascular adverse events. The cumulate incidence of VAEs was the period of TKI therapy commencement to the date of the first incidence of VAEs or the last follow-up

however, the incidence rate of CI was relatively higher in patients treated with nilotinib when the treatment agent used for TKI therapy was considered. A report from Korea showed frequent incidence of stroke during nilotinib therapy compared with dasatinib therapy [19], and this finding was supported by the result of the ENESTnd trial, which compared the efficacy and adverse events between imatinib and nilotinib in a 5-year follow-up period [2].

It is well-known that the incidence rate of CVD differs inter-racially or regionally and by gender. The rate is higher in males compared with females [16, 17] and lower in the Japanese general population compared with the European population [20]. In fact, the incidence rate of IHD and CI in males was twofold higher than for females; and in European cohort per 1000 person-years (11.9 and 43.0; mean age, 78 years) were ten times higher than that in the Japanese general population (1.8 and 3.3; mean-adjusted age, 53.1 years), although the patients' ages were considerably different [16, 17, 20]. The influence of TKI on VAE development should be detailed with a longer follow-up period in each region.

In this study, three cases of VAEs were reported in dasatinib-treated patients. In a report by le Coutre et al., it was revealed that the risk of peripheral arterial disease was low in dasatinib-treated patients [21]. In contrast, from the results of the DASISION study, IHD incidence rate was higher in dasatinib-treated patients [5]. Furthermore, meta-analysis of several clinical studies showed that VAE risks among dasatinib-treated patients were the same as those treated with nilotinib [9]. In this analysis, dasatinib possibly

Table 3 Incidence rates of VAEs in TKI-treated patients per 1000 person-years in comparison with age-matched general population in Japan

	General population	CML patient ($N = 369$)			Imatinib ($N = 199$)			Nilotinib ($N = 140$)			Dasatinib ($N = 143$)		
	Incidence rate[a]	Events	Exposure time (years)	Incidence rate[a]	Events	Exposure time (years)	Incidence rate[a]	Events	Exposure time (years)	Incidence rate[a]	Events	Exposure time (years)	Incidence rate[a]
All VAEs		25	2287	10.93	9	1336	6.74	12	464	25.86	3	411	7.30
IHD	1.787[b]	13	2287	5.68	4	1336	2.99	7	464	15.09	2	411	4.87
CI	3.342[c]	8	2287	3.50	3	1336	2.25	3	464	6.47	1	411	2.43
PAOD	N/A	4	2287	1.75	2	1336	1.50	2	464	4.71	0	411	0

VAE vascular adverse event, *TKI* tyrosine kinase inhibitor, *CML* chronic myeloid leukemia, *IHD* ischemic heart disease, *CI* cerebral infarction, *PAOD* peripheral arterial occlusive disease, *N/A* not available, *AMI* acute myocardial infarction

[a] Incidence rate per 1000 person-years

[b] Takashima AMI Registry, 1990–2001. (2008) American Journal of Epidemiology, 167(11):1358–1364

[c] Takashima Stroke Registry, 1988–2004. (2010) Stroke, 41(9), 1871–1876

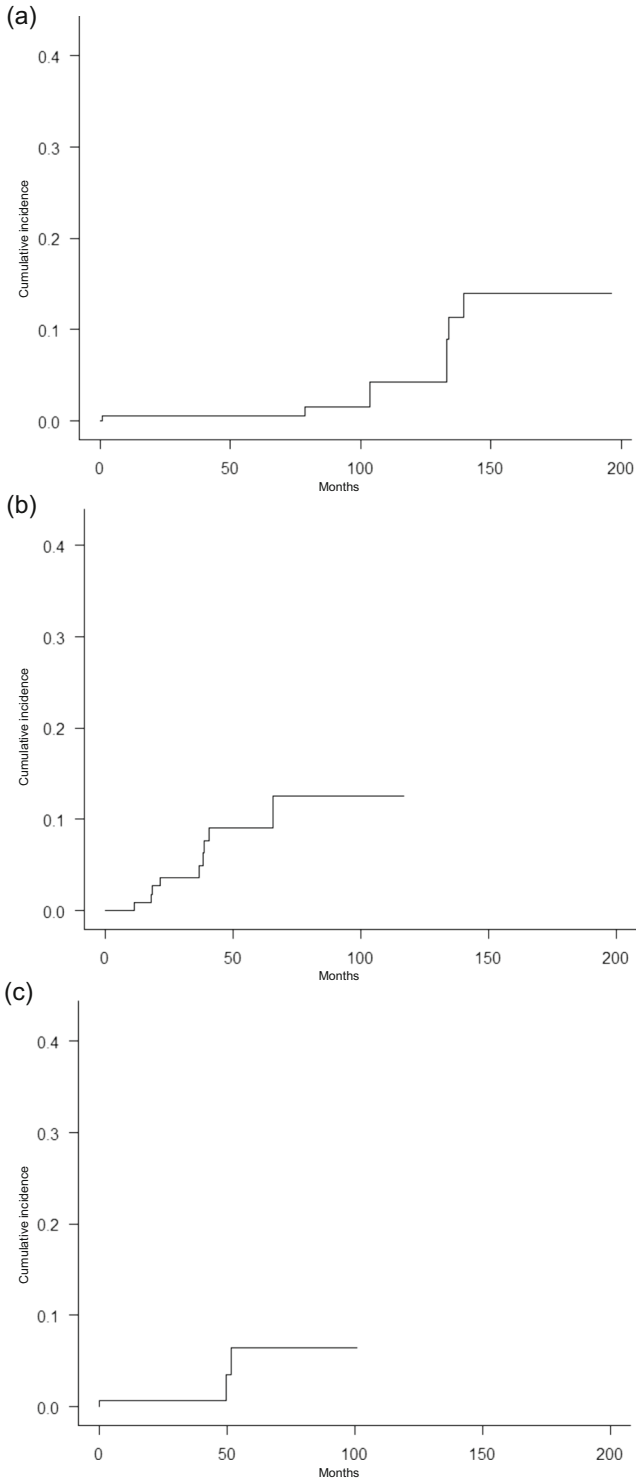

Fig. 2 Cumulative incidence of vascular adverse events during imatinib (**a**), nilotinib therapy (**b**), and dasatinib therapy (**c**). Patients who had been given both imatinib and nilotinib were included in both arms during each treatment period

increased the risk of IHD; however, further estimation of the cases was needed. We hypothesize that racial or regional differences possibly influenced the profile of VAE during TKI therapy. Of note, two patients developed CI at young ages (patient #14, 35 years; and #18, 39 years). The incidence rate of IHD among nilotinib-treated patients was higher in our study population, although three of 12 events were developed while being treated with lower doses (150–300 mg), while the other nine were given 600 mg per day. VAE incidence during nilotinib therapy is reported to be associated with therapy dose and Framingham risk [2]. Patient selection based on the VAE risk assessment, early treatment intervention, and strict management of underlying diseases such as hypertension, dyslipidemia, and diabetes mellitus should be carefully considered. In addition, verification of preventive effects of anti-platelet therapy is warranted, and low-dose TKI treatment, which is aimed at reducing VAE incidence, is worth considering; and ankle brachial pressure index is also a useful test for evaluating the dynamics of VAE risk during TKI therapy and is recommended [22, 23].

Our analysis showed insufficient efficacy of the Suita score in predicting VAE incidence, which was developed for the prediction of CVD in the Japanese population. Such a result implies that the underlying mechanism of VAE during TKI therapy might be different from the mechanism of arteriosclerosis-related CVD. Nilotinib treatment reportedly causes an upregulation of adhesion protein levels in human endothelial cells, resulting in induction of pro-atherogenic changes and angiogenesis reduction [24]. Consequently, these changes suppress proliferation and cause further decline in endothelial cell functions. Nilotinib reportedly decreased miR-3121-3p levels and induced IL-1β expression in vascular endothelial cells that stimulated the monocyte adhesion [25]. In vitro experiments performed using human endothelial cell line demonstrated the above-mentioned findings, but the detailed mechanism is yet to be consolidated; however, such evidence provides a clue to CVD development during TKI therapy. Collectively, these results suggest that novel CVD risk assessment tools employing endothelial damage-related factors can contribute toward improving CVD risk assessment during TKI therapy, to some extent. Of note, the comparisons of CV risk between different TKIs were compromised because this study was a retrospective analysis and included the following limitations: insufficient number of patients who developed VAEs and seven patients were pretreated with other TKIs.

In conclusion, the incidence of VAEs in the Japanese population, particularly of IHD, is more frequently observed among patients treated with nilotinib than among those treated with imatinib or dasatinib. Furthermore, the predictive ability of currently available CVD risk assessment tools may be insufficient for risk stratification in patients treated with TKIs, particularly the Suita score. At present, clinicians require early therapeutic interventions for detecting hypertension, dyslipidemia, and diabetes mellitus to strictly control these diseases. However, the antecedent TKIs might have influenced the development of VAEs, because six out of ten patients who

developed VAE during nilotinib therapy had been pretreated with other TKIs (five with imatinib and one with dasatinib). The influence of antecedent therapy on the development of VAE should be investigated in the future. In addition, further investigation of molecular mechanisms and development of new technology for evaluating endothelial cell damages may contribute toward treatment optimization and risk stratification during TKI therapy.

Compliance with ethical standards

The study was approved by the research ethics boards of each institution participating in the study and was conducted in accordance with the Declaration of Helsinki.

Ethical approval For this type of study, formal consent is not required.

Conflict of interest Author Tomoiku Takaku has received a speaker honorarium from Bristol-Myers Squibb, Novartis Pharma K.K, Pfizer Inc. Noriyoshi Iriyama has received a speaker honorarium from Bristol-Myers Squibb. Michihide Tokuhira has received a speaker honorarium from Bristol-Myers Squibb and Pfizer Inc. Tatsuya Kawaguchi has received a speaker honorarium from Novartis Pharma K.K.

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