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Short communication

Recurrent arterial occlusive events in patients with chronic myeloid leukemia treated with second- and third-generation tyrosine kinase inhibitors and role of secondary prevention

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ABSTRACT

Background: Risk of death is particularly high in patients with a previous history of arterial occlusive events (AOEs) and the probability for a recurrent event is around 20%. Little is known about recurrent AOE and the role of secondary prevention in patients with Chronic Myeloid Leukemia (CML) with previous AOE, treated with second- and third-generation tyrosine kinase inhibitors ($2^{ndG}/3^{rdG}$ TKIs), nilotinib, dasatinib, bosutinib and ponatinib.
Methods: We identified a real-life cohort of 57 consecutive adult CML patients treated with $2^{ndG}/3^{rdG}$ TKI. All patients had a previous history of AOE. Ongoing use of secondary prevention of AOE (including antiplatelet agents, anticoagulant therapy, and statins) before starting a $2^{ndG}/3^{rdG}$ TKI was recorded, as well as CV risk factors.
Results: The 60-month cumulative incidence rate of recurrent AOEs was 47.8 ± 10.9%. Despite a history of AOE, 10 patients (16%) were not receiving secondary preventative measures. Patients treated with nilotinib and ponatinib showed a higher incidence of recurrent AOEs (76.7 ± 14.3% and 64 ± 20.1%, respectively) than those treated with dasatinib and bosutinib (44 ± 24.2% and 30.5 ± 15.5%, respectively) ($p = 0.01$). Only treatment with a $2^{ndG}/3^{rdG}$ TKI given as second or subsequent line therapy showed a significant association with an increased incidence of recurrent AOE ($p = 0.039$). Overall, 17 recurrent AOEs were observed; 3 CV-related deaths were reported.
Conclusion: CML patients with a previous history of AOE treated with $2^{ndG}/3^{rdG}$ TKI represent a particular patient population with a higher probability of experiencing a recurrent AOE; individualized treatment is needed to optimize secondary prevention.

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1. Introduction

Cardiovascular disease (CVD) remains the most important cause of death worldwide, and is responsible for a third of all deaths before the age of 65 [1]. Risk of death is particularly high in patients with a previous history of CVD. Data from a large cohort of such patients showed that the mean estimated risk rate for a recurrent vascular event was 20%, which increased with age (from 10% for patients aged <50 years to 32% for those >70 years) [2]. Nilotinib, dasatinib, bosutinib and ponatinib are second- and third-generation tyrosine kinase inhibitors ($2^{ndG}/3^{rdG}$ TKIs) effective in the treatment of chronic myeloid leukemia (CML), but are potentially associated with cardiovascular (CV) complications; their use in patients with pre-existing CVD requires caution [3–6]. CML patients with a history of CVD represent a challenge for clinicians and thus far, limited information is available regarding the incidence of recurrent arterial occlusive events (AOEs) in patients treated with $2^{ndG}/3^{rdG}$ TKIs, associated risk factors, and the role of secondary prevention.

We therefore reported a real-life cohort of Italian CML patients treated with $2^{ndG}/3^{rdG}$ TKIs outside clinical trials, with a previous history of CVD. The primary endpoint was to establish the incidence of recurrent arterial occlusive events (AOE)s and the association with risk factors. Secondary endpoints were to evaluate the role of secondary prophylaxis in preventing AOEs and to report the management of AOEs complications in the clinical practice.

2. Methods

We identified 57 consecutive adult patients with CML who were initiated on a $2^{ndG}/3^{rdG}$ TKI between 2012 and 2017 in 17 Italian centers. All patients had a previous history of AOE, including myocardial infarction, angina, stroke, peripheral artery disease, and ischemic cerebrovascular events. Ongoing use of therapeutic measures for secondary prevention of AOE (including antiplatelet agents, anticoagulant therapy, and statins) before starting a $2^{ndG}/3^{rdG}$ TKI was recorded. Tobacco use, systolic blood pressure, and presence of diabetes, over-weight (body mass index > 24.9 kg/m^2), mild or severe renal insufficiency, and dyslipidemia were also recorded. All patients underwent a cardiologic consultation with echocardiography and ECG at baseline; 65% of them were also evaluated with routine carotid and iliac ultrasound; all patients with early signs of arterial damage during TKI treatment were addressed for a vascular consultation.

The probability of developing AOEs over the stated period of time of 60 months (cumulative incidence) was estimated after starting $2^{ndG}/3^{rdG}$ TKI treatment.

Multivariate analyses were performed using the Cox proportional hazards regression model in order to explore CV risk factors, $2^{ndG}/3^{rdG}$ TKI treatment variables (type of TKI, dosage standard vs reduced, and line of treatment), secondary prevention measures, and incidence of recurrent AOEs. The log-rank test was used to compare two or more groups of stratified patients. A p-value <0.05 was considered statistically significant. Data analysis was performed using a standard statistical package (SPSS for Macintosh, Version 21, Chicago, IL).

3. Results

The CV patients' characteristics are summarized in Table 1. The median age at initiation of $2^{ndG}/3^{rdG}$ TKI treatment was 52 years (range, 45–87). All patients were evaluated according to the Sokal score, a prognostic model that evaluates the risk of leukemia progression, on the basis of age, spleen size, platelet and blast cell count at baseline [7].

The Sokal score was intermediate to high in 43.9% of patients. The majority of patients reported a history of myocardial infarction/angina (63%), followed by subclinical atheromatous disease (15.8%), stroke (14%), and peripheral arterial occlusive disease (PAOD) (7%). Subclinical atheromasia was identified during baseline ultrasound before starting TKI treatment [8].

At the beginning of $2^{ndG}/3^{rdG}$ TKI treatment, a drug for secondary prevention of AOE was being utilized in 47 patients (84%). Despite a history of AOE, 10 patients (16%) were not receiving secondary preventative measures.

Sixteen patients (28%) received a 2^{ndG} TKI as frontline treatment for CML: 2 received nilotinib, 12 dasatinib, and 2 bosutinib; 41 (72%) patients were treated with a $2^{ndG}/3^{rdG}$ TKI as a second or subsequent line of therapy: 8 received nilotinib, 13 dasatinib, 10 bosutinib, and 10 ponatinib. The reasons for a subsequent line of TKI therapy were inefficacy of a previous TKI in 73.7% and intolerance in 26.3% of patients. The median time between initiating a $2^{ndG}/3^{rdG}$ TKI and the onset of a recurrent AOE was 21.1 months (range, 1–38).

The 60-month cumulative incidence rate of recurrent AOEs was 47.8 ± 10.9%. Patients treated with nilotinib and ponatinib showed a higher incidence of recurrent AOEs (76.7 ± 14.3% and 64 ± 20.1%, respectively) than those treated with dasatinib and bosutinib (44 ± 24.2% and 30.5 ± 15.5%, respectively) ($p = 0.01$) (Fig. 1). In multivariate analysis only treatment with a $2^{ndG}/3^{rdG}$ TKI given as second or subsequent line therapy showed a significant association with an increased incidence of recurrent AOE ($p = 0.039$).

Overall, 17 recurrent AOEs were observed (29.8%) (Table 1); Among them, 2 patients reported a worsening of carotid atheromasia from baseline ultrasound, while a patient with a previous myocardial infarction complained of a symptomatic carotid artery plaque; 3 out 4 patients (75%) with myocardial infarction had a history of previous myocardial infarction; 2 out 7 patients (28.5%) with PAOD had e previous PAOD event; none patient with stroke reported a previous stroke.

Nine AOEs were graded as 3–4 according to the common toxicity criteria, and 3 CV-related deaths were reported.

Following the recurrent AOEs, 4 patients did not require dose modification, 2 patients reduced the dose, and 11 patients discontinued the treatment. Several patients were required to undergo additional diagnostic tests such as electrocardiography, cardiac ultrasound, peripheral vascular Doppler ultrasound, and cardiac magnetic resonance angiography/computed tomography angiography; 5 patients underwent coronarography, and 2 patients required invasive procedures such as percutaneous transluminal angioplasty and coronary stent application. One patient underwent percutaneous transluminal coronary angioplasty (PTCA), had a history of previous myocardial infarction. Additional medical therapy was introduced in the majority of cases.

4. Discussion

AOEs represent off-target relevant complications of $2^{ndG}/3^{rdG}$ TKIs [9]. Given the long-term (often lifelong) TKI treatment required by the majority of CML patients, who today can expect survival similar to that of the general population [10], an individualized treatment approach based also on CV safety and quality of life is needed [11]. This is crucial for CML patients with a previous history of AOE. Indeed, this study showed a higher incidence of recurrent AOEs in patients treated with a $2^{ndG}/3^{rdG}$ TKI (5-year incidence = 47.8%) in comparison with the rate found in cardiovascular patients across European countries (10-year incidence = 20%) [2]. Sequential treatment with 2 or more $2^{ndG}/3^{rdG}$ TKIs was confirmed as a predictive risk factor for recurrent AOEs. In this complex scenario, dasatinib and bosutinib seemed more manageable.

A striking data from real world is that percentage of patients treated with antiplatelet therapy and statins, despite a previous AOE, is low and not in accordance with cardiologic recommendation of intensive treatment of such patients for secondary prevention. Moreover, the finding is even more interesting considering that CML patients received an additional risk factor for AOE, that is TKI treatment. Practical recommendation emphasizes that patients received a clinical (vascular or cardiologic consultation) or imaging evaluation at baseline (i.e., echocardiography, ECG, carotid ultrasound, stress ECG test) to define their risk and optimize therapy. Moreover, early signs of arterial damage during TKI treatment should be investigated (for example, by a routine carotid ultrasound) [5].

With changing population demographics, the increasing prevalence of more complex cardiac conditions, and the availability of new target therapies with CV off-target effects, effective secondary prevention of AOE represents a challenge [12]. Preventative measures include lifestyle

Table 1
Cardiovascular profile of 57 CML patients with a history of arterial occlusive events and management of 17 recurrent arterial occlusive events after $2^{ndG}/3^{rdG}$ TKI treatment.

	N°	(% out 57 pts)		N°	(% out 57 pts)
CML patients with previous AOE	57		Line of TKI during recurrent AOE		
			First line	2	(3.5)
Median age at diagnosis, years (range)	52	(45–87)	Subsequent line	15	(26.3)
CV risk factors			TKI during recurrent AOE		
Hypertension	24	(42.1)	Nilotinib	7	(12.3)
Dyslipidemia	32	(56.1)	Dasatinib	3	(5.3)
Over-weight (BMI > 24.9)	33	(57.9)	Ponatinib	4	(7)
Severe renal insufficiency	1	(1.8)	Bosutinib	3	(5.3)
Diabetes	25	(43.9)			
			Toxicity grading adverse events		
AOE before TKI treatment			Grade 1–2	5	(8.8)
Myocardial infarction/angina	36	(63.2)	Grade 3–4	9	(15.8)
Subclinical atheromatous disease[a]	9	(15.8)	Grade 5	3	(5.3)
Stroke	8	(14)			
PAOD[b]	4	(7)	TKI dose modification		
			Unchanged	4	(7)
Secondary AOE prevention			Reduced	2	(3.5)
Antiplatelet	46	(80.7)	Interrupted	11	(19.3)
Anticoagulant	1	(1.8)			
Statin	19	(33.3)	Additional tests requested		
			Coronarography	5	(8.8)
Line of treatment with $2^{ndG}/3^{rdG}$ TKI			ECG/cardiac ultrasound	4	(7)
First line	16	(28.1)	Cardiac MRA/CTA	5	(8.8)
Second line	25	(43.9)	Peripheral vascular Doppler ultrasound	5	(8.8)
Third line	12	(21.1)	None	5	(8.8)
Fourth line	4	(7)			
			Therapies introduced		
AOE following $2^{ndG}/3^{rdG}$ TKI	17	(29.8)	Coronary stents	2	(3.5)
Myocardial infarction/angina	4	(7)	PTA[c] peripheral artery	4	(7)
PAOD	7	(12.3)	Antiplatelet	4	(7)
Stroke	3	(5.3)	Anticoagulant	5	(8.8)
Atheromatous disease[a]	3	(5.3)	Antihypertensive[d]	4	(7)
			No further action	5	(8.8)

CVD: cardiovascular disease; AOE: arterial occlusive event; $2^{ndG}/3^{rdG}$ TKIs: second- and third-generation tyrosine kinase inhibitors; MRA/CTA: cardiac magnetic resonance angiography/computed tomography angiography.
[a] Carotid, coronary, aortic.
[b] Peripheral arterial occlusive disease.
[c] PTA (percutaneous transluminal angioplasty).
[d] Diuretics, calcium channel blockers, ACE inhibitors, and beta blockers.

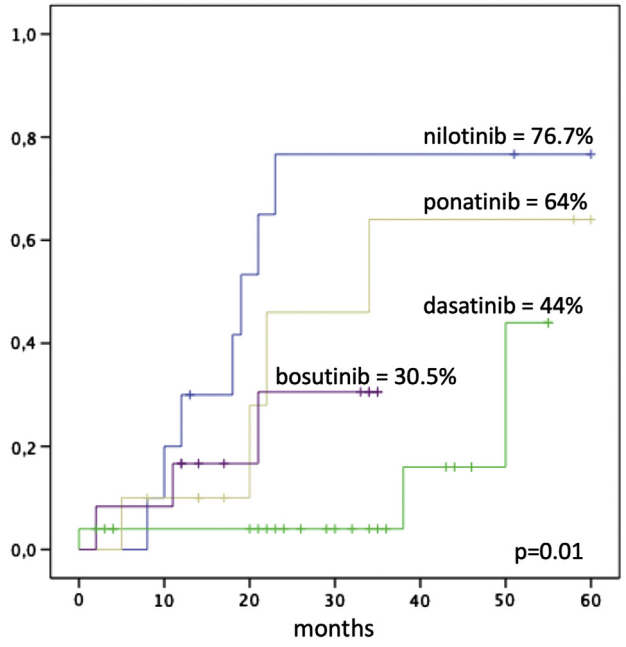

Fig. 1. Cumulative incidence of recurrent arterial occlusive events in 57 patients with a previous history of cardiovascular disease (10 treated with nilotinib, 10 with ponatinib, 25 with dasatinib, and 12 with bosutinib).

interventions (smoking, diet, physical activity), control of blood pressure, lipid, and glucose profiles, and adherence to cardio-protective drugs (in our cohort from real-life clinical practice, 16% of patients were not receiving cardio-protective drugs however). Moreover, CV rehabilitation programs have been suggested as effective and applicable, and should be proposed as a part of a multidisciplinary approach to CML management [12].

In conclusion, CML patients with a previous history of AOE treated with $2^{ndG}/3^{rdG}$ TKI represent a particular patient population with a higher probability of experiencing a recurrent AOE; individualized treatment is needed to optimize secondary prevention. This aim requires the availability of a cardio-oncology facility, being cardio-oncology a discipline based on the collaboration between cardiologists, hematologists and other medical specialists with the aim of preventing, monitoring, diagnosing and treating AOE before, during and after treatment.

Ethics approval and consent to participate

Data on patients were retrospectively collected in accordance with the 1975 guidelines of the Declaration of Helsinki.

Competing interests

The other authors have no conflicts of interest to disclose.

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