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ORIGINAL ARTICLE

Renin angiotensin system inhibitors reduce the incidence of arterial thrombotic events in patients with hypertension and chronic myeloid leukemia treated with second- or third-generation tyrosine kinase inhibitors

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Abstract

Hypertension is a commonly reported comorbidity in patients diagnosed with chronic myeloid leukemia (CML), and its management represents a challenge in patients treated with 2nd- or 3rd-generation tyrosine kinase inhibitors (TKIs), considering their additional cardiovascular (CV) toxicity. The renin angiotensin system (RAS) contributes to hypertension genesis and plays an important role in atherosclerosis development, proliferation, and differentiation of myeloid hematopoietic cells. We analyzed a cohort of 192 patients with hypertension at CML diagnosis, who were treated with 2nd- or 3rd-generation TKIs, and evaluated the efficacy of RAS inhibitors (angiotensin-converting enzyme inhibitors (ACEi) and angiotensin-II receptor blockers (ARBs)) in the prevention of arterial occlusive events (AOEs), as compared with other drug classes. The 5-year cumulative incidence of AOEs was 32.7 ± 4.2%. Patients with SCORE ≥ 5% (high-very-high) showed a significantly higher incidence of AOEs (33.7 ± 7.6% vs 13.6 ± 4.8%, $p = 0.006$). The AOE incidence was significantly lower in patients treated with RAS inhibitors (14.8 ± 4.2% vs 44 ± 1%, $p < 0.001$, HR = 0.283). The difference in the low and intermediate Sokal risk group was confirmed but not in the high-risk group, where a lower RAS expression has been reported. Our data suggest that RAS inhibitors may represent an optimal treatment in patients with hypertension and CML, treated with 2nd or 3rd[G] TKIs.

Keywords Chronic myeloid leukemia · Arterial occlusive events · TKI · Hypertension · Renin angiotensin system inhibitors

Introduction

The natural history of chronic myeloid leukemia (CML) has dramatically changed since the introduction of tyrosine kinase inhibitors (TKIs), and currently survival of CML patients parallels the general population [1, 2]. Nevertheless, TKI treatment is burdened by potential endocrine, metabolic, and cardiovascular (CV) toxicity [3, 4]. Among CV comorbidities, hypertension has been shown to be strongly linked with CV diseases risk and, consequently, with the vascular mortality [5]. In the general adult population, the overall prevalence of hypertension is around 30–45% and represents a frequent CV

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comorbidity reported in patients diagnosed with CML [6]. Second (2nd) and third generation (3rd^G) tyrosine kinase inhibitors (TKIs) nilotinib and ponatinib have been associated with hypertension, due to off-target inhibition of vascular endothelial growth factor receptor (VEGFR) [7]. In addition, other well-known mechanisms play a key role in regulating endothelial cells, such as the renin angiotensin system (RAS) [8]. Interestingly, previous studies showed that RAS can promote proliferation and differentiation of hematopoietic cells and also play a potential role in development of hematological disorders [9, 10]. In particular, a locally activated bone marrow RAS seems implicated in neovascularization of endothelial progenitors and in promoting atherosclerosis [11–13]. Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin-II receptor blockers (ARBs) are active in RAS system and represent milestone treatments of hypertension. Consolidate evidences show that RAS inhibitors (ACEi and ARBs) can prevent CV accidents when used alone or in combination with other antihypertensive drugs [14].

Despite the above-mentioned CV toxicity of TKIs, no data is still available on the optimal treatment of patients with hypertension at CML diagnosis. The primary endpoint of our study was to evaluate the role of RAS inhibitors (ACEi and ARBs) in comparison with other available treatments, in the prevention of arterial occlusive events (AOEs) in a large cohort of CML patients receiving 2nd and 3rd^G TKIs and with known hypertension.

Patients and methods

We evaluated patients with a known hypertensive status at diagnosis of chronic phase CML, between July 2007 and July 2017, in 22 Italian centers. Patients were stratified according to the Sokal index, used to predict survival at the time of CML diagnosis before starting treatment, and based on age, spleen size, platelet count, and percentage of myeloblasts in the peripheral blood. CV risk factors to assess the Systematic Coronary Risk Evaluation (SCORE), a 10-year risk estimation of fatal CV disease based on sex, age, smoking, systolic pressure, and total cholesterol level, were collected at baseline [15]. Other CV risk factors were also considered such as increased body mass index > 24.5 kg/m^2, diabetes, dyslipidemia, mild, or severe renal insufficiency. A positive anamnesis of CV diseases was reported, including angina, myocardial infarction, stroke, arterial hypertension, heart arrhythmia, heart failure, aortic aneurysms, cardiomyopathy, valvular heart disease, ischemic cerebrovascular events, thromboembolic disease, peripheral artery disease, and venous thrombosis. Primary or secondary antithrombotic prophylaxis was registered. All AOEs onset after the start of a 2nd or 3rd^G TKIs were registered. Percentages derived from univariate analysis were compared using the X^2 test. Probabilities of overall survival (OS) and cumulative incidence of AOEs were estimated by the Kaplan-Meier method; the log-rank test was used to compare two or more groups of stratified patients. Multivariate analysis was performed with a Cox proportional hazards regression model. The study was conducted in accordance with the Declaration of Helsinki.

Results

A total of 192 patients with known hypertension at diagnosis of CML were considered. All patients received 2nd or 3rd^G TKIs in first or subsequent treatment lines. The characteristics of patients are shown in Table 1. The median follow-up since CML diagnosis was 5 years (range 0.8–12). The median age at diagnosis was 63 years (range 37–89) and 56.3% of patients were male. The Sokal score was high in 28.6% and low-intermediate in 71.4% of patients.

Eighty-six patients (44.8%) received a 2nd TKI as first line of treatment, and 106 (55.2%) were treated with subsequent lines of 2nd or 3rd^G TKIs. Overall, 72 patients (37.5%) received nilotinib, 64 patients (33.3%) dasatinib, 29 patients (15.1%) bosutinib, and 27 patients (14.1%) ponatinib.

All patients had a previous history of hypertension at CML diagnosis. Concomitant CV diseases or CV risk factors are listed in Table 1. Fifty-one patients (26.6%) had a primary and twenty-four (12.5%) a secondary atherothrombotic prophylaxis. Overall, 106 patients (55.2%) were classified at a high/very high CV risk according to the SCORE system. Hypertension treatment was based on RSA inhibitors in 71.9% of patients (ACEi in 85 and ARBs in 53 patients); the remaining 28.1% were treated with calcium channel blockers, thiazide diuretics, beta-blockers, and doxazosin.

Overall, after the start of a 2nd or 3rd^G TKIs, 28 AOEs were registered, including peripheral arterial disease, myocardial infarction/angina, and stroke. The 5-year cumulative incidence of AOEs was 32.7 ± 4.2%. Patients with SCORE ≥ 5% (high-very-high) showed a significantly higher incidence of AOEs (33.7 ± 7.6% vs 13.6 ± 4.8%, $p = 0.006$). The cumulative incidence of AOEs was significantly lower in patients treated with RAS inhibitors (ACEi and ARBs) when compared with other anti-hypertension drugs (14.8 ± 4.2% vs 44 ± 1%, $p < 0.001$) (Fig. 1). A protective role of RAS inhibitors was confirmed by multivariate analysis (HR = 0.283, C.I. 95% = 0.131–0.612, $p = 0.001$). A subdivision of patients by Sokal index confirmed a RAS inhibitors' protective role in the low- and intermediate-risk group (6.7 ± 0.4% vs 44.6 ± 2.3%, $p = 0.026$ and 11.8 ± 0.7% vs 44.5 ± 1.2%, $p = 0.001$, respectively) but not in the high-risk group (30 ± 1% vs 59 ± 2.9%, $p = 0.592$). We also evaluated the role of different TKIs on AOE incidence, and in comparison with a group of 48 CML patients (median age 69 years, range 46–85) with

Table 1 Characteristics of patients and cardiovascular profile of 192 patients with hypertension at diagnosis of Chronic Myeloid Leukemia

Sex, *N* (%)			**CV risk factors**, *N* (%)		
Male	108	(56.3)	Dyslipidemia	80	(41.7)
Female	84	(43.7)	Obesity (BMI > 24.5)	95	(49.5)
Age at diagnosis, median years (range)	63	(37–89)	Severe renal insufficiency	3	(1.6)
Follow-up, median years (range)	5	(0.8–12)	Diabetes	43	(22.4)
Leukocyte × 10^3/μL, median value (range)	156	(8–344)	**CVD disease before TKIs**, *N* (%)		
Hemoglobin g/dL, median value (range)	12	(5–17.4)	Myocardial infarction/ angina	15	(7.8)
Platelet × 10^3/μL, median value (range)	329	(84–2082)	Arrhythmia	7	(3.6)
BCR/ABL1 transcript type, *N* (%)			Atheromatous disease÷	11	(5.7)
e13a2 or e14a2	187	(97.4)	Stroke	2	[1]
e1a2	4	(2.1)	Peripheral arterial disease	2	[1]
e19a2	1	(0.5)	**SCORE CV score ≥ 5%**	106	(55.2)
Splenomegaly, *N* (%)	85	(44.3)	**Primary prophylaxis**	51	(26.6)
Sokal score, *N* (%)			**Secondary prophylaxis**	24	(12.5)
Low	49	(25.5)	**Positive anamnesis for AOE**	28	(14.6)
Intermediate	88	(45.8)	**AOE events following TKIs**, *N* (%)		
High	55	(28.6)	Myocardial infarction/angina	12	(6.3)
Type of TKIs, *N* (%)			Peripheral arterial disease±	14	(7.3)
Dasatinib	64	(33.3)	Stroke	2	[1]
Nilotinib	72	(37.5)	**Hypertension treatment**, *N* (%)		
Ponatinib	27	(14.1)	ACEi	85	(44.2)
Bosutinib	29	(15.1)	ARBs	53	(27.6)
Line of TKI treatment, *N* (%)			Calcium channel blocker	61	(31.8)
First line	86	(44.8)	Thiazide diuretics	50	(26)
Second line	66	(34.4)	Beta-blockers	61	(31.8)
Third line	27	(14.1)	Doxazosin	3	(1.6)
Fourth line	13	(6.8)			

CVD, cardiovascular disease; *TKIs*, tyrosine kinase inhibitors; *AOE*, arterials occlusive event; *ACEi*, angiotensin-converting enzyme inhibitors; *ARBs*, angiotensin-II receptor blockers

÷, PAOD, atheromatous carotid disease

±, PAOD, atheromatous carotid disease, thrombotic peripheral arterial

hypertension, treated with imatinib; RAS inhibitors were assumed by 56% of them.

The 5-year cumulative incidence of AOEs was significantly lower in the imatinib group in comparison with the ponatinib (8 ± 5.7% vs 30.4 ± 1.6%, $p = 0.05$) and nilotinib group (8 ± 5.7% vs 26.4 ± 6.7%, $p = 0.04$), while no statistical differences were found in comparison with the dasatinib (11.8 ± 4.6%) and bosutinib group (17.9 ± 7.3%) (Supplemental figure).

Finally, the 5-year OS in our cohort was 93.8 ± 1.7%.

Discussion

CV complications of TKI therapy represent a clinical emerging challenge in patients with CML and require a multidisciplinary approach for diagnosis and treatment. Hypertension represents an important cause of CV-related death [5]. Dysregulation of RAS pathway contributes to hypertension genesis and plays an important role in atherosclerosis development [8]. In such pathway, angiotensinogen is converted to angiotensin-I (Ang-I) by circulating renin. Subsequently, Ang-I is cleaved by the ACE to form angiotensin-II (Ang-II). Ang-II effects are mediated by two receptors, Ang-II-type-I receptor (AT1R) and Ang-II-type-2 receptor (AT2R). Whereas AT1R is associated with growth, inflammation, and vasoconstriction, AT2R is generally associated with apoptosis and vasodilation [16]. The receptors' activation leads to reduced nitric oxide (NO) synthesis, and subsequent generation of reactive oxygen species (ROS) that are proinflammatory, mitogenic, prothrombotic, and profibrotic. Taken

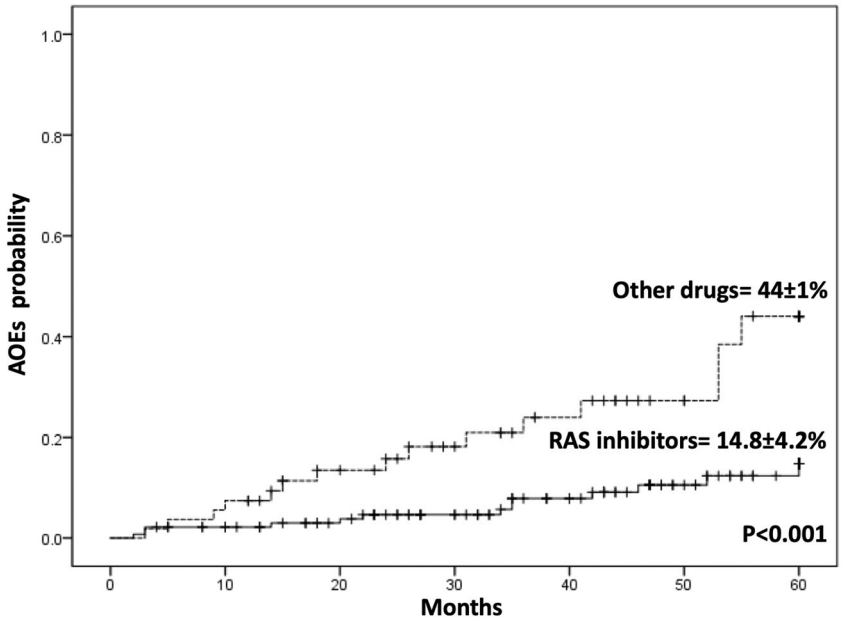

Fig. 1 Cumulative incidence of arterial occlusive events (AOEs) in CML patients with hypertension, according to treatment with RAS inhibitors or other drugs

together, these processes contribute to vascular injury, including the atherogeneous damage that underlies several cardiovascular diseases [17]. In addition, an influence on bone marrow cell proliferation has been elucidated [9, 10]. A study on CML patients treated with imatinib showed that levels of different components of the RAS pathways were more expressed in CML patient than in the normal population; in addition, lower levels of RSA components were detected in the patients belonging to the Sokal high-risk group [10].

We analyzed a large real-life cohort of patients complaining hypertension at CML diagnosis and found a relatively high 5-year incidence of AOE (33.7%). The SCORE index confirmed a prognostic significance, as reported in previous observations, and should be calculated before the start of any TKIs [18]. Since treatment-free remission (TFR) is now an emerging treatment goal for patients with CML and because several predictive factors of TFR have been proposed, predictive CV risk models may be useful to identify CML patients that could benefit from a TKI treatment interruption [19, 20].

We found a significant lower incidence of AOEs in patients with hypertension treated with RAS inhibitors (ACEi and ARBs) in comparison with other available treatments (14.8 ± 4.2% vs 44 ± 1%, $p < 0.001$) (Fig. 1). These data might suggest a role of RAS pathway in the genesis of vascular damage in CML patients treated with TKIs. In particular, nilotinib has shown to exert direct pro-atherogenic and anti-angiogenic effects on vascular endothelial cells and RAS inhibitors could contribute to reduce the vascular proinflammatory state [21].

Interestingly, the lower incidence of AOE in patients receiving RAS inhibitors was confirmed both in the low and intermediate Sokal risk group but not in the high-risk group. Given the previous in vitro observation that lower levels of RAS components were detected in high-risk Sokal group patients, we could hypothesize a lower effectiveness of RAS inhibitors in preventing AOEs in such group.

In conclusion, our data suggest that RAS inhibitors (ACEi and ARBs), in comparison with other anti-hypertension drugs, may represent an optimal treatment for CML patients treated with 2nd or 3rd^{G} TKIs, in particular in those belonging to a low or intermediate Sokal risk group. These data should be confirmed in further studies.

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Collection and assembly of data: GC, OM, FS, MB, MA, LL, EO, EA, NS, BM, FA, SG, PP, MB, FC, MT, GB, AG, IC, CF, DL, FE, MPS, LS, FDG, CE, MMT, DC, IA, CB, FP, AS, GG, RS, ES, AI, RF, MB, GLN
Statistical analysis: GC, OM, FE
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Compliance with ethical standards

Competing interests The authors declare that they have no conflicts of interest.

Ethics approval and consent to participate Data on patients were retrospectively collected in accordance with the 1975 guidelines of the Declaration of Helsinki.

Consent for publication Not applicable

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