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ORIGINAL ARTICLE

Incidence and evaluation of predisposition to cardiovascular toxicity in chronic myeloid leukemia patients treated with bosutinib in the real-life practice

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Abstract

There is little information about cardiovascular adverse event (CV-AE) incidence in chronic myeloid leukemia (CML) patients treated with bosutinib in the real-life practice. We identified 54 consecutive CML patients treated with bosutinib, stratified according to the Systematic Coronary Risk Evaluation (SCORE) assessment, based on sex, age, smoking habits, systolic blood pressure, and total cholesterol levels. The 40-month cumulative incidence of CV-AEs was 25.2 ± 8.1%. Patients with the SCORE of high–very high showed a significantly higher incidence of CV-AEs (55 ± 12.9% vs 9 ± 9.5%; $p = 0.002$). Overall, 9 CV-AEs were reported, with 2 deaths attributed to CV-AE. In conclusion, the SCORE assessment before starting treatment is helpful in identifying CV-AE high-risk patients during bosutinib treatment.

Keywords Chronic myeloid leukemia · Bosutinib · Cardiovascular risk · Acetylsalicylic acid

Introduction

Bosutinib is a second-generation tyrosine kinase inhibitor (TKI) with significant activity against chronic myeloid leukemia (CML), through ABL1 inhibition without affecting PDGFR or c-KIT activity [1]. Bosutinib is reported to be relatively well tolerated, with rare cardiovascular (CV) toxicity reports in sponsored clinical trials [2]. In the BELA trial, the

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incidence of CV adverse events (AEs) was similar between patients receiving bosutinib and those treated with imatinib (10%) [3]. A phase II study, reporting a large cohort of CML patients who were resistant or intolerant to imatinib and other previous TKIs, and who had been administered a 500 mg/day bosutinib dose, showed 18% of cardiac and 13% of vascular events [4]. A recent study collecting a series of 62 patients from the real-life practice, who had undergone third/fourth-line treatment, reported only 4% of patients experiencing a vascular event [5].

Nevertheless, accumulating evidence suggested that the combination of a median age at CML diagnosis ≥ 60 years, when CV-AEs are common, and the coexistence of other CV risk factors, represented potential predisposing factors that needed preventive strategies before treatment and strict CV surveillance during therapy [6]. Practical management guidelines for the treatment of CML patients with bosutinib have been published recently [7].

Previous studies suggested the usefulness of the Systematic Coronary Risk Evaluation (SCORE) assessment at disease baseline—a 10-year risk estimation of fatal CV disease based on sex, age, smoking, systolic pressure, and total cholesterol level—in identifying patients at heightened risks of CV-AE during TKI treatment [8–11].

With the primary aim to evaluate the incidence of CV-AEs and their association with the SCORE assessment and other baseline risk factors, we analyzed a cohort of Italian CML patients treated with bosutinib in the real-life setting. Secondary objectives were to evaluate the role of primary prophylaxis in preventing CV atherothrombotic events and to report management of CV complications in clinical practice.

Methods

We retrospectively analyzed the data of 54 consecutive adult patients with chronic phase CML who started bosutinib outside clinical trials after resistance or intolerance to imatinib or other TKIs, between January 2012 and December 2017 in 14 Italian centers.

To stratify the patients according to the SCORE risk, all data collected relating to age, sex, tobacco use (smokers vs non-smokers), systolic pressure, and total cholesterol serum level were evaluated before administering bosutinib; patients were thus stratified in low–moderate (SCORE ≤ 5%) or high–very high CV risk (SCORE > 5%) [6]. Other CV risk factors were also considered including increased body mass index > 24.5 kg/m^2, diabetes mellitus, dyslipidemia, and mild or severe renal insufficiency. Comorbidities at CML diagnosis were collected, as well as a positive anamnesis of CV diseases including angina pectoris, stroke, myocardial infarction, arterial hypertension, heart failure, heart arrhythmia, cardiomyopathy, aortic aneurysms, valvular heart disease, ischemic cerebrovascular events, peripheral artery disease, thromboembolic disease, and venous thrombosis. Ongoing primary antithrombotic prophylaxis before starting bosutinib, based on the presence of previous risk factors and represented by acetylsalicylic acid 100 mg/day, was another clinical data recorded from chart review. All CV-AEs were registered after starting bosutinib in any line of treatment and data regarding their management by the hematologists and cardiologists were collected.

CML response to TKIs was evaluated according to the 2013 European LeukemiaNet recommendations [12]. Molecular response was estimated by the presence of detectable BCR-ABL1 transcripts using qRT-PCR with a sensitivity of 3 logs (MR^3) or deeper (MR^4) [13].

The probability of cumulative incidence of CV-AEs was estimated after starting bosutinib. The log-rank test was used to compare two or more groups of stratified patients. We evaluated the impact of the following variables on the incidence of CV-AEs: positive previous history of CV-AE, age ≥ 60 years, bosutinib dose, number of TKI treatment lines, SCORE risk, and primary prophylaxis with acetylsalicylic acid 100 mg/day. Multivariate analysis was performed using the Cox proportional hazards regression model. 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).

Results

Data of 54 CML patients were retrospectively analyzed. Patients' characteristics are shown in Table 1. Median age at diagnosis was 54 years (range, 23–89) with 50% being females. The Sokal score was intermediate/high in 62.9% of patients. The median follow-up since CML diagnosis was 6 years (range, 1.2–23.6). The reasons for switching to bosutinib were inefficacy (40.7%) and intolerance to the previous line of therapy (59.3%). The median time of exposure to bosutinib was 16.5 months (range, 6–40).

Table 1 reports the CV risk factors and CV diseases registered among CML patients prior to bosutinib treatment. Assessment of the SCORE risk showed that 57.4% of patients were classified in the low–intermediate (SCORE ≤ 5%) and 42.6% in the high–very high (SCORE > 5%) categories.

The 40-month cumulative incidence of CV-AEs was 25.2 ± 8.1%. The median time between the start of bosutinib and the occurrence of a CV-AE was 10 months (range, 2–21) while the median intensity dose was 358 mg/day (range, 100–500 mg/day). Patients with a SCORE of high–very high showed significantly higher incidence of CV-AEs (55 ± 12.9% vs 9 ± 9.5%; p = 0.002) (Fig. 1). Also, patients aged ≥ 60 years or with a positive history of CV disease showed higher incidence of CV-AEs (40 ± 13.5% vs 4.9 ± 5.7%; p = 0.04 and 36.9 ± 11.8% vs 6.4 ± 6.4%; p = 0.05, respectively).

Table 1 Characteristics of 54 CML patients treated with bosutinib

	N°	%
Sex		
Male	27	(50)
Female	27	(50)
Age at diagnosis, median years (range)	53	(23–89)
Follow-up, median years (range)	6	(1.2–23.6)
Bcr/Abl transcript type		%
p210	51	(94.4)
p190	3	(5.6)
Sokal score		
Low	20	(37)
Int	22	(40.7)
High	12	(22.2)
Line of treatment		
Second line	26	(48.1)
Third line	21	(38.9)
Fourth line	7	(13)
Bosutinib dose per day		
100 mg	2	(3.7)
200 mg	10	(18.5)
300 mg	18	(33.3)
400 mg	5	(9.3)
500 mg	19	(35.2)
TKI sequence		
Ima-Bosu	21	(38.9)
Dasa-Bosu	4	(7.4)
Nilo-Bosu	1	(1.9)
Ima-Dasa-Bosu	13	(24.1)
Ima-Nilo-Bosu	7	(13)
Nilo-Ima-Bosu	1	(1.9)
Ima-Nilo-Dasa-Bosu	5	(9.3)
Ima-Dasa-Nilo-Bosu	2	(3.7)
Reason of switch		
Inefficacy	22	(40.7)
Intolerance	32	(59.3)
Time exposure to bosutinib, median months (range)	16.5	(1–40)

TKI, tyrosine kinase inhibitor; *Ima*, imatinib; *Bosu*, bosutinib; *Nilo*, nilotinib; *Dasa*, dasatinib

In multivariate analysis, we analyzed the association between CV-AEs and previous history of CV-AE, age ≥ 60 years, bosutinib dose, number of TKI treatment lines, SCORE risk, and primary prophylaxis; only the SCORE risk maintained a significant association ($p = 0.009$).

Atherothrombotic AEs (myocardial infarction, angina pectoris, ischemic cerebrovascular events, and peripheral vascular disease) were registered in 6 patients: 4 following imatinib and 2 following dasatinib, respectively. No significant difference in atherothrombotic AE incidence was found in patients who underwent acetylsalicylic acid prophylaxis before starting bosutinib.

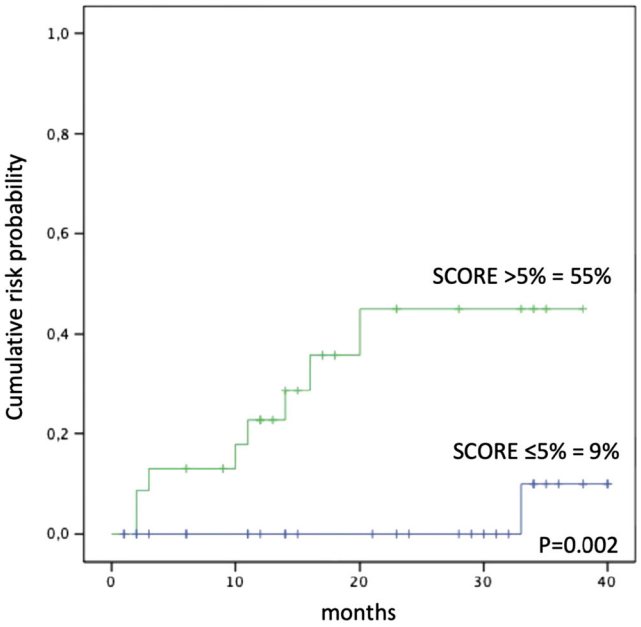

Fig. 1 Cardiovascular adverse event incidence in 54 CML patients treated with bosutinib, according to the SCORE risk

Overall, 9 CV-AEs were observed during bosutinib treatment (9 second-line-treated patients: 6 following imatinib and 3 after dasatinib, respectively).

The median time to CV-AEs was 10 and 3 months after a change to bosutinib in the group treated with imatinib-bosutinib and dasatinib-bosutinib sequences, respectively. No patient underwent nilotinib before bosutinib. We did not find any significant difference between CV-AE incidence and line of bosutinib treatment or previously administered TKI.

Their management in real-life practice is described in Table 2. A grade 3–4 toxicity was reported in 5 cases, and 2 deaths were attributed to CV-AE by physicians.

Overall, in 55.6% of 9 observed CV-AEs, bosutinib treatment did not require dose modification; 11.1% of patients reduced the dose and 33.3% of them discontinued the treatment. The majority of patients reporting CV-AEs required additional diagnostic tests such as ECG/cardiac ultrasound, peripheral vascular Doppler, or cardiac angio-MR/CT; one patient required CT coronarography procedure. Additional medical therapy was introduced in 4 patients; one patient required percutaneous transluminal angioplasty as an invasive procedure. The 5-year cumulative incidence of MR[4] was 68.1 ± 8.4% and it was not significantly influenced by the CV-AE occurrence.

Discussion

CV-AEs represent off-target relevant complications of the second- and third-generation TKI treatment, but their incidence

Table 2 Cardiovascular profile of 54 patients and management of 9 cardiovascular adverse events

	N°	(%) out of 54 pts		N°	(%) out of 54 pts
CV risk factors			*Line of treatment at CV-AEs*		
Hypertension	18	(33.3)	Second line	9	(16.7)
Dyslipidemia	16	(29.6)	Third line	0	(0)
Obesity (BMI > 24.5)	29	(53.7)	Fourth line	0	(0)
Severe renal insufficiency	1	(1.9)			
Diabetes mellitus	16	(29.6)	*TKI sequence at CV-AEs*		
			Imatinib-bosutinib	6	(11.1)
SCORE* ≤ 5% (low–int.)	31	(57.4)	Dasatinib-bosutinib	3	(5.6)
SCORE > 5% (high–very high)	23	(42.6)			
			Toxicity grading CV-AEs		
CVD before bosutinib			Grades 1–2	2	(3.7)
Myocardial infarction/angina pectoris	7	(15)	Grades 3–4	5	(9.3)
Arrhythmia	3	(5.6)	Grade 5	2	(3.7)
Other cardiac diseases[∞]	2	(3.7)			
Peripheral arterial disease	0	(0)	*Total deaths CV-AEs related*	2	(3.7)
Cerebrovascular stroke	2	(3.7)			
Hypertension	18	(33.3)	*Bosutinib dose modification*		
Peripheral venous disease	0	(0)	Unchanged	5	(9.3)
Primary prophylaxis[+]	15	(27.8)	Reduced	1	(1.9)
Secondary prophylaxis**	11	(20.4)	Interrupted	3	(5.6)
CVD events following bosutinib			*Additional test requested*		
Number of CVD events	9	(16.7)	Coronarography	1	(1.9)
Myocardial infarction/angina pectoris	2	(3.7)	ECG/cardiac ultrasound	5	(9.3)
Arrhythmia	1	(1.9)	Cardiac angio-MR/TAC	3	(5.6)
Hypertension	0	(0)	Peripheral vascular Doppler	0	(0)
Other cardiac disease[×]	2	(3.7)	Nothing	5	(9.3)
Peripheral arterial disease[±]	1	(1.9)			
Cerebrovascular stroke	3	(5.6)	*Therapy-introduced*		
Peripheral venous disease	0	(0)	Coronary stents	0	(0)
			PTA peripheral artery	1	(1.9)
Bosutinib dose at CV-AEs			Antiplatelet	1	(1.9)
100 mg	0	(0)	Anticoagulant	1	(1.9)
200 mg	3	(5.6)	Antiarrhythmic	1	(1.9)
300 mg	3	(5.6)	Other drugs[®]	1	(1.9)
500 mg	3	(5.6)	No further action	5	(5.6)

CVD, cardiovascular disease; *CV-AEs*, cardiovascular adverse events

*Based on sex, age, smoking, systolic pressure, and cholesterol level

[∞] Valvulopathy, dilatative cardiomyopathy

[+] Based on the presence of CV risk factors and represented by acetylsalicylic acid 100 mg/day

**Secondary to positive history of atherothrombotic event and represented by acetylsalicylic acid, clopidogrel, and ticlopidine

[×] Pericardial effusion, cardiac arrest, and pulmonary hypertension

[±] Atheromasic carotid disease

PTA (percutaneous transluminal angioplasty)

[®] Calcium channel blockers, ACE inhibitor, and beta blockers

is variable and still not well defined [14]. Cardiac and vascular toxicities long-term evaluation in bosutinib-treated patients in the first-line and relapsed/refractory settings were reported with a low incidence [15]. Particularly, data from two large clinical trials showed 6.8% (3.7% grade ≥ 3 CTC) of vascular AE and 9.5% (3.9% grade ≥ 3 CTC) of cardiac AE [15]. Notably,

Table 3 Characteristics of 12 patients treated with low dose of bosutinib

N	Sex	Sokal score	Age	Prior TKI	Reason of change from previous TKI	Cardiovascular comorbidities	SCORE risk	Dose of bosutinib	Months of bosutinib	Best molecular response	Cardiovascular adverse event
1	F	Int.	81	Imatinib Dasatinib	Inefficacy	Hypertension	Low–moderate	200 mg	30	Less than MR^3	Myocardial infarction
2	F	Low	57	Imatinib	Intolerance	–	Low–moderate	200 mg	14	MR^4	–
3	M	Low	54	Dasatinib	Intolerance	–	High–very high	200 mg	2	MR^3	–
4	M	High	85	Imatinib	Inefficacy	Hypertension, myocardial infarction	High–very high	200 mg	2	Less than MR^3	Stroke
5	F	High	76	Imatinib	Intolerance	Hypertension	Low–moderate	100 mg	9	MR^3	–
6	F	Int.	83	Imatinib	Inefficacy	Hypertension	Low–moderate	200 mg	1	Less than MR^3	–
7	F	High	89	Imatinib	Intolerance	Hypertension, arrhythmia	Low–moderate	200 mg	6	MR^4	–
8	M	Int.	74	Imatinib	Inefficacy	Myocardial infarction, cerebrovascular stroke, peripheral arterial disease	High–very high	200 mg	11	MR^4	–
9	M	Low	76	Imatinib	Inefficacy	–	High–very high	100 mg	28	MR^4	–
10	F	Low	80	Imatinib	Intolerance	–	Low–moderate	200 mg	2	MR^4	–
11	M	Low	49	Imatinib Nilotinib Dasatinib	Intolerance	–	Low–moderate	200 mg	12	MR^4	–
12	F	Int.	70	Imatinib	Inefficacy	–	Low–moderate	200 mg	14	Less than MR^3	–

TKI, tyrosine kinase inhibitor; *MR*, molecular response

patients in both studies were excluded if they had a history of uncontrolled cardiac diseases (including congestive heart failure, uncontrolled angina pectoris or hypertension within 3 months, myocardial infarction within 12 months, and clinically significant ventricular arrhythmia) or required medications known for prolonging QT interval. Presently, there is little information about CV-AE incidence in bosutinib-treated CML patients in real-life practice. Recent data published by the Grupo Español de Leucemia Mieloide Cronica reported 30% CV-AEs during treatment with other TKIs and only 3 cases of vascular events after starting bosutinib, following intolerance or resistance to previous lines of therapy. This information should be treated with caution since the median time to bosutinib was only 9 months and the first CV-AEs in previous studies with other TKIs appeared after longer drug exposure [5].

Here, we observed a 40-month cumulative CV-AE incidence of 25.2% and median time of bosutinib exposure of 16.5 months (range, 6–40).

We found that the SCORE assessment before starting treatment is helpful in identifying CV-AE high-risk patients during bosutinib treatment. Overall, these observations suggested the need of personalized treatment approaches with every TKI, suggesting an appropriate stratification and consideration of CV risk factors at baseline. Twelve patients included in this study were treated outside of any recommended dose range of bosutinib (10 patients with 200 mg and even 2 patients with 100 mg only; Table 3). In the real-life scenario, physicians move toward a tailored therapy considering comorbidities and individual patient characteristics.

Due to the low number of events, we were unable to show a role of primary prophylaxis with acetylsalicylic acid in preventing atherothrombotic complications, but these data should be confirmed in future studies [9].

In conclusion, the management and treatment of patients with high–very high SCORE risk before starting any TKI should require the availability of a cardio-oncology facility and a close collaboration between cardiologists, hematologists, and other medical specialists with the aim of preventing, monitoring, diagnosing, and treating CV-AE before, during, and after treatment [9, 16].

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Authors' contributions Conception and design: GC and MB
Collection and assembly of data: GC, OM, EA, AI, MA, EO, SG, GB, NS, LL, BM, ARR, MB, CF, MMT, DC, CE, CB, FDG, MM, GLN, RF, and MB
Statistical analysis: GC, OM, and FE
Manuscript writing: GC and MB
Final approval of the manuscript: GC, OM, EA, AI, MA, EO, SG, GB, NS, LL, BM, ARR, MB, CF, MMT, DC, CE, CB, FDG, MM, GLN, RF, and MB

Data availability Data and medical charts are available at the Italian institutions involved in the study.

Compliance with ethical standards

Competing interests The authors declare that they have no conflict 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.

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