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Cardiovascular toxicity in patients with chronic myeloid leukemia treated with second-generation tyrosine kinase inhibitors in the real-life practice: identification of risk factors and the role of prophylaxis

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To the Editor:

Long-term treatment with the second-generation tyrosine kinase inhibitors (2^{ndG}TKIs) nilotinib and dasatinib may result in cardiovascular (CV) complications. Accumulating evidence suggests that the combination of a median age at the time of chronic myeloid leukemia (CML) diagnosis of greater than 60 years, when CV adverse events (AEs) are common, and the CV toxicity of 2^{ndG}TKIs represents *per se* a potential predisposing factor, which requires preventive strategies and CV surveillance in patients with CML [1-3]. Previous studies have 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 habits, systolic blood pressure, and total cholesterol levels, to identify patients who are at heightened risk of CV AEs during nilotinib treatment [4-5]. A preventive strategy with primary prophylaxis based on aspirin remains under discussion. We therefore analyzed a large real-life cohort of Italian patients with CML treated with a 2^{ndG}TKIs as first- or subsequent-line of treatment. The primary objective was to evaluate the incidence of CV AEs and the association with the SCORE assessment and other baseline risk factors. The secondary objectives were to evaluate the role of primary prophylaxis in preventing CV atherothrombotic events.

We identified consecutive adult patients with CML who initiated nilotinib or dasatinib as first- or subsequent-line treatment, between January 2012 and December 2015 in 20 Italian centers. Patients were stratified into low-moderate (SCORE ≤5%) or high-very high (SCORE >5%) CV risk. Additional risk factors were the presence of diabetes, body mass index > 24.5 kg/m^2, mild or severe renal insufficiency, and dyslipidemia. Patients were also evaluated for comorbidities and a positive anamnesis of CV diseases, including angina, myocardial infarction, stroke, heart failure, arterial hypertension, cardiomyopathy, heart arrhythmia, valvular heart disease, aortic aneurysms, ischemic cerebrovascular events,

peripheral artery disease, thromboembolic disease and venous thrombosis. The presence of antithrombotic prophylaxis before initiating CML treatment was also recorded. The probability of the cumulative incidence of CV and atherothrombotic AEs was estimated after initiating treatment with 2^{ndG}TKIs. The cumulative incidence of deep molecular response (MR^4) was evaluated from the initiation of 2^{ndG}TKIs treatment. Multivariate analyses were performed using the Cox proportional hazards regression model.

A total of 506 patients with CML were retrospectively recruited. The patients' characteristics are shown in supplemental table 1. The mean age at diagnosis was 52 years (range 18-87) and 57% were men. Sokal score was intermediate-high in 55% of patients. The mean follow-up time since CML diagnosis was 5.4 years (range 0.2-23). Overall, 286 patients were treated with nilotinib and 220 with dasatinib. 2^{ndG}TKIs were administered as first-, second-, and third-line treatment in 61%, 32%, and 7% of cases, respectively. The reasons for switching treatments in 196 patients were inefficacy in 63.8%, intolerance in 29.6%, and protocol requirements in 6.6%. The majority of patients (93%) were classified as at low-intermediate risk (SCORE ≤5%) and 7% as at high-very high risk (SCORE>5%). A positive history for CV diseases was noted in 181 (35.8%) patients. The 60-month CV AE cumulative incidence registered in the total cohort of patients was 21.7±2.8%. Patients treated with nilotinib and dasatinib showed CV AE incidence of 24.7±3.9% and 16.4±3.7%, respectively (p=0.25; NS) (Supplemental figure 1). Patients treated with 2^{ndG}TKIs administered as first- or second-line of treatment and as subsequent-line treatment showed a CV AE incidence of 12.9±3.5% and 22.9±4.4%, respectively (p=0.004). Patients with high-very high SCORE showed significantly high incidence of CV AEs (46.6±16.6% vs. 20±2.8%; p<0.001).

The mean time between the initiation of 2^{ndG}TKI treatment and the occurrence of CV AEs was 35.5 (range 1-69) months. Overall, 68 CV AEs were registered, with 2 event-related

deaths; 40% of CV AEs were graded as 3/4 of common toxicity criteria. Supplemental table 2 reports the CV AEs and their management in the real-life. We did not find any association between TKI dose and CV AE incidence. The frequency of peripheral arterial disease (PAOD or atheromasic carotid disease) was significantly high in patients undergoing nilotinib treatment. Two patients died due to myocardial infarction during treatment. Overall, in 44% of cases 2^{ndG}TKI treatment did not require dose modification; 16% of patients reduced the dose and 40% of them discontinued the treatment. The majority of patients required additional diagnostic tests as ECG/cardiac ultrasound, peripheral vascular Doppler or cardiac angio-MR/CT; 7 patients underwent coronarography procedure and 13 patients required invasive procedures as percutaneous transluminal angioplasty or application of coronary stents.

The 5-year cumulative incidence of MR^4 following 2^{ndG}TKIs treatment was 69.9±2.6% and it was not significantly influenced by CV AE occurrence.

Multivariate analysis showed that a positive history of CV diseases (p=0.002; hazart ratio (HR)=2.3, 95% confidence interval (C.I.)=1.3-3.8) and treatment with 2^{ndG}TKIs administered as second-line or beyond (p=0.002; HR 2.3, 95% C.I.=1.3-3.5) was significantly associated with a high incidence of CV AEs (Supplemental table 3). We stratified patients using a simple score based on positive anamnesis for CV disease and a treatment with 2^{ndG}TKIs administered as second-line or beyond. Patients with none or one factor were considered to be at standard risk; patients with both factors were considered to be at high-risk of CV AEs. The CV AE incidence was significantly higher in patients with a CML-CV high-risk score, with both risk factors, compared with that in patients with none or one factor (45.9±8.2% vs 16.3±4.4% and 18.7±3.9%, p<0.001) (Figure 1).

Atherothrombotic diseases (myocardial infarction, angina, ischemic cerebrovascular events and peripheral vascular disease) were registered in 44 (8.7%) of patients. The

atherothrombotic AE incidence was 13.1±2.5%. Considering patients aged ≥60 years with high CML-CV risk score, the atherothrombotic AE incidence was significantly lower in 6 patients who were treated with 100 mg/day of aspirin compared to that in 34 patients who did not undergo primary prophylaxis (0% vs. 58.2±18.9%; p=0.01) (Supplemental Figure 2). Aspirine was administered for a median of 54 (range 21-64) and 46 (range 5-64) months to the group with and without CV AEs, respectively. Overall, we also found a trend towards a lower atherothrombotic AE incidence in 10 patients of varying ages with high CML-CV risk score who were treated with 100 mg/day of aspirin compared to that in the 59 patients who did not undergo primary prophylaxis (0% vs. 33.9± 9.5%; p=0.11).

CV AEs represent off-target relevant complications of 2^{nd} and 3^{rdG} TKI treatment [6,7].

Our study showed that a positive history for CV diseases and treatment with 2^{ndG}TKIs administered as second-line or beyond was significantly associated with a higher incidence of CV AEs. Indeed, patients with both risk factors showed a 5-year CV-AE incidence of 45.9%, which was significantly higher compared to that in patients with no or only one risk factor. Therefore, we suggest that this simple score (CML-CV total risk=2) represents an easy-to-use and rapid tool to identify patients with an increased risk of developing CV AEs if treated with nilotinib or dasatinib. These patients could benefit from switching to another TKI with a lower CV risk profile (imatinib or bosutinib), avoiding sequential administration of 2^{ndG}TKIs or combining rotation therapy between 1^{st} and 2^{ndG}TKIs. Treatment discontinuation could represent a goal in CV high-risk patients with a stable and durable MR^4 who meet minimal criteria for discontinuing treatment.

The role of aspirin is debatable and no conclusive data have been published thus far. In patients aged ≥60 years with a CML-CV high risk=2 treated with 100 mg/day of aspirin, however, we observed a significantly lower incidence of atherothrombotic AEs compared to

that in those without primary prophylaxis. Future prospective studies are needed to further corroborate our preliminary findings.

In conclusion, our findings emphasize the need to personalize prevention strategies based on CV risk factors. Data on the efficacy of primary prophylaxis in patients with high-risk CV-CML score are promising, but need to be confirmed in prospective randomized trials.

DECLARATIONS

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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Authors' contributions:

Conception and design: GC, MB. Collection and assembly of data: GC, OM, MA, LL, MB, EO, PP, SG, ARR, EA, AI, BM, NS, GB, FC, AG, CF, MB, AS, FS, EU, FDG, LS, CE, FP, CB, MMT, DC, CL, GG, MM, GS, GLN, RF, MB. Statistical analysis: GC, OM, FE. Manuscript writing: GC, MB. Final approval of manuscript: GC, OM, MA, LL, MB, EO, PP, SG, ARR, EA, AI, BM, NS, GB, FC, AG, CF, MB, AS, FS, FE, EU, FDG, LS, CE, FP, CB, MMT, DC, CL, GG, MM, GS, GLN, RF, MB

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Figure legends

Figure 1. Cardio-vascular adverse event incidence in 436 patients with standard risk (0 or 1 risk factor considering age ≥60 years and treatment with 2^{ndG}TKIs administered as second-line or beyond) and 70 patients with high-risk CML- cardiovascular score (both risk factors were present).
2ndGTKI, second-generation tyrosine kinase inhibitor; CML, chronic myeloid leukemia.

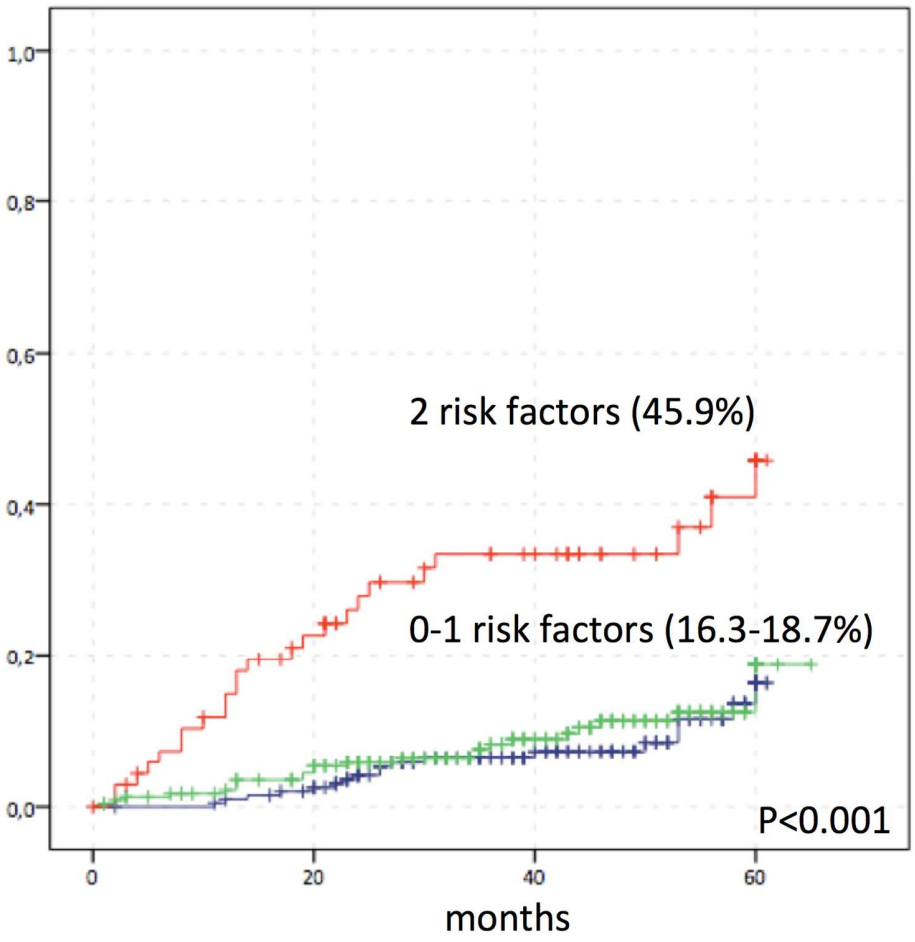

Figure 1

267x264mm (144 x 144 DPI)