Manuscript Details

Manuscript number	IJC_2019_3552_R1
Title	Long-term mortality rate for cardiovascular disease in 656 chronic myeloid leukaemia patients treated with second- and third-generation tyrosine kinase inhibitors
Article type	Short communication

Abstract

Background. Limited information is available regarding the rate of long-term cardiovascular (CV) mortality in chronic myeloid leukaemia (CML) patients treated with second- and third-generation tyrosine kinase inhibitors (2ndG/3rdG TKIs) in the real-life practice. Methods. We identified 656 consecutive CML patients treated with nilotinib, dasatinib, bosutinib and ponatinib. Results. The 15-year CV-mortality free survival was 93±2.8%. Age ≥65 years (p=0.005) and a positive history of CV disease (p=0.04) were significantly associated with a lower CV-mortality free survival. CV disease accounted for 16.5% and 5% of potential years of life lost (PYLL) in male and female patients, respectively. The standard mortality ratio (SMR) following ischemic heart disease (IHD) was 3.9 in males and 3.8 in female patients, meaning an excess of IHD deaths observed, in comparison with the population of control. Conclusion. Prevention strategies based on CV risk factors, in particular in those patients with a previous history of CV disease, should be considered.

Keywords	Chronic Myeloid Leukemia; Cardiovascular toxicity; TKI; ischemic heart disease; PYLL
Taxonomy	Ischemic Heart Disease
Manuscript region of origin	Europe

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Research Data Related to this Submission

There are no linked research data sets for this submission. The following reason is given:
Data will be made available on request

Dear Editor,

please find attached our “Long-term mortality rate for cardiovascular disease in 656 chronic myeloid leukaemia patients treated with second- and third-generation tyrosine kinase inhibitors”.

Limited information is available regarding the rate of long-term cardiovascular (CV) mortality in chronic myeloid leukaemia (CML) patients treated with second- and third-generation tyrosine kinase inhibitors (2^{ndG}/3^{rdG} TKIs) in the real-life practice. We identified a “real life” cohort of 656 consecutive Italian CML patients treated with nilotinib, dasatinib, bosutinib and ponatinib.

CV disease accounted for 16.5% and 5% of potential years of life lost (PYLL) in male and female patients, respectively. The standard mortality ratio (SMR) following ischemic heart disease (IHD) revealed an excess of IHD deaths observed, in comparison with the Italian population of control.

Prevention strategies based on CV risk factors, in particular in those patients with a previous history of CV disease, should be considered.

All authors have contributed in a significant manner and are in agreement with all content in the manuscript; there are no conflicts of interest to disclose. This paper has not been sent elsewhere and we hope you may find it worthy of publication in your Journal.

Yours sincerely

Giovanni Caocci and Massimo Breccia

Response to reviewer

Dear Editor,

As suggested, we carefully considered the new comments made by the reviewer and answered point by point

Reviewer#1

The manuscript "Long-term mortality rate for cardiovascular disease in 656 chronic myeloid leukaemia patients treated with second- and third-generation tyrosine kinase inhibitors" is a practical report and has merit to be publish in IJC. Despite of to be a retrospective analysis with data obtained from the petients' records, the paper contains data from 656 patients treated with TKi of 2nd and 3rd generation, about of 50% as front line and the other 50% as 2nd line due to efficacy (32%) or intolerance (18%). The data are from 19 Centers and have a good median follow up of 6 years. The most important conclusion is the higher risk of CV events in patients over 65 y.o. and presenting previous CV diseases.

Answer: thank you for your encouraging comment

Reviewer#2

We know that the cardiotoxicity of the various types of TKIs (Dasatinib, Nilotinib, Ponatinib and Bosutinib) is different, for this reason the authors should indicate the percentage of AOE events for each of them. In particular, if it is possible, the incidence of myocardial infarction/angina, peripheral arterial disease and stroke for each drug. This is very important because the incidence of cardiotoxicity of Ponatinib seems to be worse than Nilotinib, Bosutinib seems to be less cardiotoxic and Dasatinib can provoke pulmonary hypertension

Answer: we added the following statement in the text and added a supplementary table

A chi-square test of independence was performed to examine the relation between AOEs and different TKIs. Nilotinib and ponatinib were significantly associated to peripheral arterial disease compared to dasatinib and bosutinib (7.3% and 5.9% versus 1.7% and 1.6%, respectively; p=0.02), while bosutinib and ponatinib showed higher association with stroke compared with nilotinib and dasatinib (5% and 3% versus 0.7% and 0%, respectively; p=0.01). No significant differences among different TKIs were found in relation with myocardial infarction/angina.

AOE	**Nilotinib** N=287	(%)	**Dasatinib** N=225	(%)	**Bosutinib** N=60	(%)	**Ponatinib** N=84	(%)	p. value
Myocardial infarction/ angina	1	0.3	4	1.7	2	3.3	2	2.3	0.18
Peripheral arterial disease	21	7.3	4	1.7	1	1.6	5	5.9	**0.02**
Stroke	2	0.7	0	0	3	5	3	3.5	**0.01**

Supplemental table. Relation between AOEs and different TKIs in 656 CML patients.

Highlights

Limited information is available on the CV mortality rate in patients with CML

Age over 65 and a previous CV disease were correlated with a worse CV-free survival

The contribution of CV disease to PYLL in CML was not higher than in the controls

IHD determined a SMR greater than expected in a standard population

Abstract

Background. Limited information is available regarding the rate of long-term cardiovascular (CV) mortality in chronic myeloid leukaemia (CML) patients treated with second- and third-generation tyrosine kinase inhibitors ($2^{ndG}/3^{rdG}$ TKIs) in the real-life practice.

Methods. We identified 656 consecutive CML patients treated with nilotinib, dasatinib, bosutinib and ponatinib.

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Conclusion. Prevention strategies based on CV risk factors, in particular in those patients with a previous history of CV disease, should be considered.

Short communication

Long-term mortality rate for cardiovascular disease in 656 chronic myeloid leukaemia patients treated with second- and third-generation tyrosine kinase inhibitors

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Funding: None
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Short communication

Long-term mortality rate for cardiovascular disease in 656 chronic myeloid leukaemia patients treated with second- and third-generation tyrosine kinase inhibitors

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Abstract

Background. Limited information is available regarding the rate of long-term cardiovascular (CV) mortality in chronic myeloid leukaemia (CML) patients treated with second- and third-generation tyrosine kinase inhibitors ($2^{ndG}/3^{rdG}$ TKIs) in the real-life practice.

Methods. We identified 656 consecutive CML patients treated with nilotinib, dasatinib, bosutinib and ponatinib.

Results. The 15-year CV-mortality free survival was 93±2.8%. Age ≥65 years (p=0.005) and a positive history of CV disease (p=0.04) were significantly associated with a lower CV-mortality free survival. CV disease accounted for 16.5% and 5% of potential years of life lost (PYLL) in male and female patients, respectively. The standard mortality ratio (SMR) following ischemic heart disease (IHD) was 3.9 in males and 3.8 in female patients, meaning an excess of IHD deaths observed, in comparison with the population of control.

Conclusion. Prevention strategies based on CV risk factors, in particular in those patients with a previous history of CV disease, should be considered.

Introduction.

In the high-income countries of Western Europe, cardiovascular (CV) mortality remains a global threat as the population grows and ages (1). In particular, CV diseases represent the leading cause of premature death, responsible for 35% of deaths under 75 years and 29% of deaths under 65 years, being ischemic heart disease (IHD) the leading single cause (2).

Chronic myeloid leukaemia (CML) is a myeloproliferative neoplasm that in the last decades has shown a dramatic reduction of potential years of life lost (PYLL), besides an improvement of life expectancy, that is now close to that observed in the general population for all ages (3)(4). Thus far, limited information is available regarding population-based data to examine the CV mortality rate in CML patients, showing that elderly patients had greater CV mortality rate and IHD incidence than non-cancer population (5).

We previously reported data on CV complications and CV related deaths in patients with CML treated with second- and third-generation tyrosine kinase inhibitors ($2^{ndG}/3^{rdG}$ TKIs) nilotinib, dasatinib, bosutinib and ponatinib(6)(7)(8)(9).

Therefore, we report survival data of a real-life cohort including 656 Italian chronic phase (CP)-CML patients treated with $2^{ndG}/3^{rdG}$ TKIs, in comparison with epidemiology data obtained from the Italian population. The primary endpoint was to establish the incidence of mortality related to CV adverse events and the PYLL parameter. The secondary endpoint was to evaluate the standardized mortality ratio (SMR) following IHD.

Methods

We considered 656 adult CP-CML patients diagnosed and treated consecutively with $2^{ndG}/3^{rdG}$ TKI, frontline or with subsequent lines of treatment in 19 Italian centres, between 2012 and 2017. Information on baseline CV risk factors prior to starting a $2^{ndG}/3^{rdG}$ TKIs treatment were retrospectively collected from the review of medical charts. All patients were evaluated at diagnosis for tobacco use, systolic pressure, and total cholesterol serum

level; additional risk factors which were taken into consideration are were as follows: presence of diabetes, body mass index >24.5 kg/m^2, mild or severe renal insufficiency, and dyslipidemia. Patients were also evaluated for concomitant comorbidities and a positive anamnesis of pre-existing CV diseases; the presence of antithrombotic primary or secondary prophylaxis was also recorded. The overall survival was estimated using the Kaplan-Meier method, from the diagnosis to the date of death from any cause. The CV- mortality free survival was estimated from diagnosis to the date of death occurred for CV complications; deaths due to progression, second tumour or other causes were considered as competing risk. The log-rank test was used to compare two or more groups of stratified patients. Multivariate analyses were 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). PYLL to CV disease provided a measure of premature mortality and was calculated by summing-up deaths occurring at each age and multiplying that result by the number of the remaining years up to the selected age limit of 75 years (10). The SMR was used to compare the mortality risk following IHD of the cohort of CML patients to that of the Italian population (11). An SMR greater than 1.0 indicates that there were "excess deaths" compared to what was expected.

Results.

Characteristics of 656 CML patients are shown in Table 1. Mean age at diagnosis was 53 years (range 18-89) and 56.7% of the patients were males. Sokal score was intermediate/high in 42.7% of patients. The mean follow-up since CML diagnosis was 6 years (range 0.6-25.9). Overall, 287 patients were treated with nilotinib, 225 with dasatinib, 84 with ponatinib and 60 with bosutinib; $2^{ndG}/3^{rdG}$ TKIs were given in first line in 50% of patients. Remaining 50% of patients were treated in second or subsequent line of treatment,

and the reason for that switching was inefficacy in 32% and intolerance in 17.8% of the cases. Table 1 also shows CV risk factors and CV diseases registered before to starting a $2^{ndG}/3^{rdG}$ TKIs treatment. History for CV disease was positive in 98 (14.9%) patients. Primary prophylaxis with aspirin was given in 16% of the patients; secondary prophylaxis with antiplatelet, anticoagulant or statin was present in 7% of the patients. Forty-eight patients (7.3%) reported arterial occlusive events (AOEs) following a $2^{ndG}/3^{rdG}$ TKIs treatment; 9 patients (1.4%) reported IHD.

A chi-square test of independence was performed to examine the relation between AOEs and different TKIs. Nilotinib and ponatinib were significantly associated to peripheral arterial disease compared to dasatinib and bosutinib (7.3% and 5.9% versus 1.7% and 1.6%, respectively; p=0.02), while bosutinib and ponatinib showed higher association with stroke compared with nilotinib and dasatinib (5% and 3% versus 0.7% and 0%, respectively; p=0.01). No significant differences among different TKIs were found in relation with myocardial infarction/angina (Supplemental table).

Overall 37 deaths were recorded. The 15-year OS was 83.3±3.6% (Supplemental figure).

Twelve deaths were related by physicians to CV complications. The 15-year CV-mortality free survival was 93±2.8% (Figure 1). Patients aged ≥65 years showed a significant lower CV-mortality free survival (72.1±13.1% vs 95.8±2.7, p<0.001). In multivariate analysis, age ≥65 years (p=0.005) and a positive history of AOEs (p=0.04) were confirmed to be significantly associated with a lower CV-mortality free survival.

Table 2 shows PYLL and SMR following IHD registered in the cohort of CML patients. Overall, 176 years of PYLL were summed up. As expected in CML patients, the major cause of PYLL was leukaemia progression (57.4% in males and 60% in females). CV diseases accounted for 16.5% in male and 5% in female patients. Data from European WHO Mortality Database showed in Italian population a contribution of CV disease to PYLL

equal to 18% in males and 12% in females (2). The SMR following IHD in CML patients treated with $2^{ndG}/3^{rdG}$ TKI was 3.9 in male patients and 3.8 in female patients. An SMR greater than 1.0 indicates that there were "excess deaths" compared to what was expected in the Italian population of control (11). The difference in SMR was particularly evident in males over 75 years and in females over 65 years.

Discussion

The accumulated evidence suggest that the combination of median age at CML diagnosis greater than 60 years, when CV adverse events are common, and the intrinsic CV toxicity related to $2^{ndG}/3^{rdG}$ TKIs might represent potential predisposing factors needing preventive strategies and CV surveillance in CML patients (12). Patients at risk of CV disease should be actively monitored during treatment with $2^{ndG}/3^{rdG}$ TKI, owing to ischemic cardiac events that may occur as a result of an accumulation of risk factors (metabolic alterations related to treatment, hypertension, etc.) and long-term treatment with TKIs.

Although life expectancy in CML is close to that observed in the general population (3)(4), in a study of 450 CML patients treated with $1^{stG}/2^{ndG}$ TKIs, CV disease has been reported exerting the most negative impact on OS, being CML-related deaths fewer than CML-unrelated deaths (13). An analysis on a large retrospective CML cohort treated or not with imatinib showed that elderly patients had greater mortality and greater rates of IHD, stroke, peripheral arterial occlusive disease (PAOD) than non-cancer patients, independently from the treatment received (5); nevertheless this study considered only patients with aged > 66 years. So far, limited information is available regarding the long-term rate of CV mortality in CML patients treated with $2^{ndG}/3^{rdG}$ TKIs.

Our results indicated a 15-year CV-mortality free survival of 93%. Age over 65 years and a previous CV disease were two factors independently correlated with a worse CV-free survival. The contribution of CV disease to PYLL in CML patients was not higher than that expected in the normal population. IHD is the leading single cause of premature death in the high-income countries of Western Europe. In our CML cohort, IHD determined a SMR greater than expected in a standard population, especially after 65 years in females and 75 years in males.

Our data confirm that IHD remains an important potential mortal complication in CML patients treated with $2^{ndG}/3^{rdG}$ TKIs. These findings emphasize the need to personalize prevention strategies based on CV risk factors, in particular in those patients with a previous history of CV disease.

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***Sex**, N° (%)*			***CVD risk factors**, N (%)*		
Male	372	(56.7)	Hypertension	177	(27)
Female	284	(43.3)	Dyslipidemia	161	(24.5)
Age at diagnosis, mean years (range)	53	(18-89)	Obesity (BMI>24.5)	340	(51.8)
Median follow-up, mean years (range)	6	(0.6-25.9)	Severe renal insufficiency	4	(0.6)
			Diabetes	81	(12.3)
Bcr/Abl transcript type, N° (%)			Positive anamnesis for AOE	57	(8.7)
p210	627	(95.6)			
p190	26	(4)	***CVD conditions before TKIs**, N (%)*		
p230	3	(0.4)	Myocardial infarction/ angina	36	(5.5)
			Arrhythmia	11	(1.7)
***Splenomegaly**, N° (%)*	353	(53.8)	Other cardiac disease∞	29	(4.4)
			Peripheral arterial disease±	13	(2)
***Sokal score**, N° (%)*			Stroke	7	(1)
Low	284	(43.3)	Peripheral venous disease	2	(0.3)
Int	245	(37.3)			
High	36	(5.4)	Primary prophylaxis	105	(16)
			Secondary prophylaxis	47	(7.1)
***Type of TKIs**, N° (%)*					
Dasatinib	225	(34.3)	***AOE events following TKIs**, N (%)*		
Nilotinib	287	(43.7)	Myocardial infarction/angina	9	(1.4)
Ponatinib	84	(12.8)	Peripheral arterial disease±	31	(4.7)
Bosutinib	60	(9.2)	Stroke	8	(1.2)
***Line of treatment**, N° (%)*			***Deaths total**, N (%)*	37	(5.6)
First line	328	(50)	Progression disease	15	(2.3)
Second line	205	(31.2)	CV related	12	(1.8)
Third line	92	(14)	Second tumour	3	(0.5)
Fourth line	32	(4.8)	other/unknown®	7	(1)

Table I. Characteristics of patients and cardiovascular profile of 656 CML patients.

CVD= cardiovascular disease; TKIs= tyrosine kinase inhibitors; AOE= arterial occlusive events
∞ valvulopathy, restrictive cardiomyopathy, dilatative cardiomyopathy, vascular ecstasies
± PAOD, Atheromatous carotid disease, thrombotic peripheral arterial
®GVHD=2, traumatic death=1, respiratory complication=3, unknown=1

A

	Males		Females	
Death causes	**PYLL**	**PYLL %**	**PYLL**	**PYLL %**
All	176	100	80	100
Progression	101	57.4	48	60
Cardiovascular	29	16.5	4	5
Second cancer	24	13.6	0	0
Other*	22	12.5	28	35

B

Males				
Age interval	Italian mortality rate for IHD (x10.000)	Observed deaths for IHD in CML patients	Number of patients with CML	Expected deaths for IHD in CML patients
45-54	2,7	0	78	0.02
55-64	8	0	84	0.07
65-74	20,18	0	77	0.16
75+	104,52	3	50	0.52
All ages		3	289	0.77
SMR		**3,9**		
Females				
Age interval	Italian mortality rate for IHD (x10.000)	Observed deaths for IHD in CML patients	Number of patients with CML	Expected deaths for IHD in CML patients
45-54	0,49	0	55	0
55-64	1,71	0	60	0.01
65-74	6,94	1	56	0.04
75+	79,65	1	59	0.47
All ages		2	230	0.52
SMR		**3,8**		

Table 2A. Potential years of life lost (PYLL) in 656 CML patients treated with $2^{ndG}/3^{rdG}$ Tyrosine Kinase Inhibitors.
Cardiovascular diseases accounted for16.5% in male and 5% in female patients. Data from European WHO Mortality Database showed in Italian population a contribution of CVD to PYLL equal to 18% in males and 12% in females. (2)
*Graft Versus Host Disease; respiratory failure; trauma; unknown.

Table 2B. Standardized Mortality Ratio (SMR) following Ischemic Heart Disease (IHD) in CML patients treated with $2^{ndG}/3^{rdG}$ Tyrosine Kinase Inhibitors.
An SMR greater than 1.0 indicates that there were "excess deaths" compared to what was expected. (11)
IHD=ischemic heart disease

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Manuscript Title: **Long-term mortality rate for cardiovascular disease in 656 chronic myeloid leukaemia patients treated with second- and third-generation tyrosine kinase inhibitors**

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This statement is to certify that all authors have seen and approved the manuscript being submitted, have contributed significantly to the work, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission to the *International Journal of Cardiology*.

We attest that the article is the Authors' original work, has not received prior publication and is not under consideration for publication elsewhere. We adhere to the statement of ethical publishing as appears in the International of Cardiology (citable as: Shewan LG, Rosano GMC, Henein MY, Coats AJS. A statement on ethical standards in publishing scientific articles in the International Journal of Cardiology family of journals. Int. J. Cardiol. 170 (2014) 253-254 DOI:10.1016/j.ijcard.2013.11).

On behalf of all Co-Authors, the corresponding Author shall bear full responsibility for the submission. Any changes to the list of authors, including changes in order, additions or removals will require the submission of a new author agreement form approved and signed by all the original and added submitting authors.

All authors are requested to disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work. If there are no conflicts of interest, the COI should read: “The authors report no relationships that could be construed as a conflict of interest”.

AOE	Nilotinib N=287	(%)	Dasatinib N=225	(%)	Bosutinib N=60	(%)	Ponatinib N=84	(%)	p. value
Myocardial infarction/ angina	1	0.3	4	1.7	2	3.3	2	2.3	0.18
Peripheral arterial disease	21	7.3	4	1.7	1	1.6	5	5.9	**0.02**
Stroke	2	0.7	0	0	3	5	3	3.5	**0.01**

Supplemental table. Relation between AOEs and different TKIs in 656 CML patients.

Supplemental file:

Overall and cardiovascular-mortality free survival in 656 CML patients treated with $2^{ndG}/3^{rdG}$ Tyrosine Kinase Inhibitors.