Cardiovascular Toxicity in Cancer Patients Treated with Tyrosine Kinase Inhibitors: A Real-World Single-Center Experience

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Keywords

Cardio-oncology · Cardiotoxicity · Tyrosine kinase inhibitors · Chronic myeloid leukemia · Arterial stiffness

Abstract

Background: Target therapy can cause various cardiovascular complications. The aim of this study was to evaluate the burden of cardiovascular complications related to treatment with anti-BCR-ABL tyrosine kinase inhibitors (TKIs) and to determine if there are differences between the latest- and first-generation TKIs. **Methods:** A retrospective observational study was carried out on 55 patients (39 men, 16 women; mean age $\pm$ SD: 58 ± 11 years) treated with TKIs targeting Bcr-Abl for a median period of 3.5 years. Patients were divided in two groups according to the type of treatment. Group A included patients treated with latest-generation TKI (nilotinib, dasatinib, and ponatinib), while group B included patients treated with first-generation TKI (imatinib). Cardio-logical evaluation included electrocardiogram, echocardiogram with global longitudinal strain of left ventricle (GLS), and carotid ultrasound scan with arterial stiffness measurement (pulse wave velocity, PWV). Adverse cardiovascular events were recorded in both groups. **Results:** Statistical

analysis showed that cardiovascular adverse events (myocardial ischemia, peripheral artery disease, deep vein thrombosis, and pleural effusion) were significantly more frequent in group A than group B (p value = 0.044). Moreover, there was a significant reduction in GLS and PWV in group A when compared to group B (respectively, $p = 0.03$ and $p = 0.004$). **Conclusions:** Our study confirms that imatinib is a relatively safe drug, while it reveals that the latest-generation TKIs may cause a burden of cardiovascular complications. GLS and PWV allow detection of early signs of cardiac and vascular toxicity in oncohematologic patients treated with TKI, and their use is advisable.

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Introduction

Over the last decade, the development and subsequent use of new therapies in clinical practice have significantly reduced the mortality rate associated with cancer, further improving the long-term prognosis in oncohematologic patients. However, evidence shows that antineoplastic therapies are not completely safe for the cardiovascular system. In fact, several studies have revealed that anthra-

Table 1. Differences between group A and group B

Drugs	Patients, <i>n</i>
<i>Group A</i>	
New anti-BCR-ABL TKIs	
Nilotinib (53%)	30
Dasatinib (20%)	
Nilotinib/ponatinib/dasatinib (27%)	
<i>Group B</i>	
Old anti-BCR-ABL TKIs	
Imatinib: GIST (84%)	25
Imatinib: CML (16%)	
Total patients, <i>n</i>	55

Table 2. Cardiovascular risk factors of the population

	Po- pulation	Group A	Group B	Difference between groups A and B (χ^2 test)
Patients, <i>n</i>	55	30	25	
Age, years	58±11	57.27±12.38	58.96±10.95	
Male/female	32/11	21/9	18/7	
Hypertension	49%	15 (50%)	12 (48%)	<i>p</i> = 0.90
Dyslipidemia	22%	9 (30%)	5 (20%)	<i>p</i> = 0.50
Diabetes	13%	6 (20%)	3 (12%)	<i>p</i> = 0.66
Smoking	18%	10 (33%)	7 (28%)	<i>p</i> = 0.91

cyclines or other anticancer drugs have cardiotoxic effects [1]. Target therapy can also cause cardiotoxicity, but it is not clear how big this problem is [2]. Tyrosine kinase inhibitors (TKIs) are selective, and for this reason they should be less cardiotoxic than other drugs. It should be noted that they can also cause various cardiovascular toxic effects [3–5]. Particularly, two different types of toxicity are known: “on-target” and “off-target” toxicity. TKIs can be divided into two groups: latest- (second- and third-generation) and first-generation drugs.

Imatinib, a first-generation TKI, seems to be less cardiotoxic than new TKIs such as nilotinib and ponatinib which can cause accelerated atherosclerosis and thrombotic events [6]. Therefore, early detection of cardiovascular toxicity caused by these drugs is important to prevent severe complications.

In light of these considerations, the purpose of this study was to assess the potential cardiovascular side effects caused by the latest TKIs (nilotinib, ponatinib, and dasatinib) and old TKI (imatinib) in a group of patients affected by gastrointestinal stromal tumors (GIST) and

chronic myeloid leukemia (CML). In particular, we measured the side effects on the cardiac and vascular systems through an accurate clinical and instrumental evaluation using the parameters of early cardiac and vascular dysfunction (global longitudinal strain of the left ventricle [GLS] and arterial stiffness). Furthermore, we assessed the differences, in regard to the cardiotoxic profile, between latest- and first-generation TKIs.

Materials and Methods

This is a retrospective observational study. Fifty-five patients (39 men and 16 women; median age ± SD: 58 ± 11 years) affected by GIST or CML were treated with new (nilotinib, ponatinib, dasatinib) and old TKIs (imatinib). The follow-up was performed by the Department of Oncology and Hematology of the University Hospital of Palermo. The study included patients treated with ponatinib where treatment with first- and second-generation TKIs had failed. The baseline characteristics of patients were taken from their clinical notes. Patients were included in the study if:

1. age ≥18 years;
2. TKI (imatinib, nilotinib, dasatinib, ponatinib) treatment for at least 1 year;
3. normal renal and liver function;
4. ejection fraction >50% before treatment administration.

Exclusion criteria were:

1. previous treatment with chemotherapy or radiation therapy;
2. previous cardiovascular events (heart failure, angina pectoris, myocardial infarction, percutaneous or surgical coronary revascularization, cardiac arrhythmias, more than mild valve disease).

Patients were divided into two groups based on the treatment administered: group A (latest TKIs) and group B (imatinib). Group A was composed of 30 patients (21 M, 9 F; median age ± SD: 57.27 ± 12.38 years) with CML, treated with new-generation TKIs (nilotinib, ponatinib, dasatinib). Eighteen patients (60%) from this group were treated with nilotinib, 9 (30%) with dasatinib, 3 (10%) with ponatinib (Table 1). Five patients treated with nilotinib previously received imatinib and 3, dasatinib. Among patients treated with dasatinib, 4 were previously treated with imatinib, and 1 with ponatinib. All patients treated with ponatinib had been previously treated with imatinib and afterwards with dasatinib or nilotinib. Group B was composed of 25 patients (18 M, 7 F, median age ± SD: 58.96 ± 10.95 years), affected by GIST (*n* = 21; 84%) and CML (*n* = 4; 16%) treated with old-generation TKI (imatinib).

The prevalence of cardiovascular risk factors in the whole population was as follows: arterial hypertension 49%, dyslipidemia 22%, diabetes mellitus 13%, smoking 18%. Among the hypertensive patients, more than half (60%) were treated with ACE inhibitors and β-blockers. The prevalence of risk factors in the two groups at the time of the cardiac assessment is reported in Table 2.

Patients were called back during treatment to undergo a cardiology clinical and instrumental assessment including an electrocardiogram, echocardiogram, and ultrasound scan of the carotid arteries. The cardiovascular adverse events observed were myocardial infarction, stable and unstable angina pectoris, transient ischemic attack and stroke, new-onset arterial hypertension, deep

venous thrombosis (DVT), and peripheral artery disease (PAD). Also pleural effusion was observed.

Echocardiographic evaluation was carried out using a Siemens Acuson SC 2000 ultrasound system prime echocardiography machine. An assessment of the cardiac chamber dimension and an evaluation of the ventricular function were carried out according to the ASE/EACVI guidelines [7]. Left ventricular ejection fraction (LVEF) was measured with the biplane modified Simpson's method. Diastolic function was evaluated using the transmitral Doppler flow and the tissue Doppler imaging at septal and lateral mitral annulus [8]. Myocardial deformation indices (GLS) were measured in all patients using VVI software (velocity-vector-imaging, Siemens). Normal reference values were considered: $-19.8\% \pm 4.6$ for this vendor [7].

Strain analysis was performed with a semiautomatic method which required manual definition of the myocardial border after the acquisition of apical three-, four- and two-chamber views (≥ 3 cardiac cycles with frame rate between 40 and 90 frames per second). After the operator drew a line along the endocardial border and approved the tracing, the software analyzed deformations and calculated global and segmental strain values. A carotid ultrasound scan was performed with an Esaote machine (MyLab Twice) using the software QAS (quality arterial stiffness) to measure pulse wave velocity (PWV). This software based on radiofrequency automatically analyzed the subtle variation of the arterial diameter (in μm) during the cardiac cycle on the common carotid artery, 1 cm above the carotid bifurcation. Carotid PWV was expressed in meters per second. Age- and sex-specific percentiles of local carotid stiffness in a healthy population were established [9]. Preclinical atherosclerosis was defined as asymptomatic carotid plaques (thickness >1.5 cm) or increased intimal medial thickness (>0.9 mm) [10]. Quantitative variables were reported as mean and standard deviation; the differences between the analyzed groups were studied with the two-tailed Student *t*-test for independent samples. A *p* value <0.05 was considered statistically significant. Qualitative variables were reported as a percentage.

Results

The mean period of treatment of the population of patients was 3.5 years, specifically 2.5 years for group A and 4 years for group B. The overall incidence of cardiovascular adverse events (coronary artery disease [CAD], DVT, PAD, new-onset arterial hypertension) during treatment was 24% ($n = 13$). Pleural effusion was observed in 3 patients (5.4%).

Cardiovascular adverse events in group A were found in 30% ($n = 9$) of patients (CAD: $n = 5$, 16.6%; PAD: $n = 1$, 3%; DVT: $n = 1$, 3%). Pleural effusion was observed in 2 patients, 6.6%. By analyzing each group by type of treatment, we observed the following events:

1. In patients treated with nilotinib ($n = 18$) two acute coronary syndromes occurred, three episodes of angina pectoris (1 patient received PCI and 1 CABG), one PAD, one DVT;

Table 3. Cardiovascular adverse events in the studied population

CV risk factors	CV adverse events	New-onset arterial hypertension
Group A 66%	30% (17% CAD, 3% PAD, 3% DVT)	7%
Group B 64%	16% (4% ischemic cardiopathy, 8% DVT)	4%

Table 4. Echocardiographic parameters and arterial stiffness index

	Group A	Group B	<i>p</i> value
LVEF	59.70 $\pm$ 5	60.12 $\pm$ 3.02	0.71
Septal E'	7.66 $\pm$ 3.02	9.14 $\pm$ 1.41	0.03
Septal S'	8.83 $\pm$ 1.98	8.44 $\pm$ 1.03	0.38
Lateral E'	10.11 $\pm$ 3.62	11.10 $\pm$ 2.09	0.23
Lateral S'	9.89 $\pm$ 2.37	9.13 $\pm$ 1.42	0.16
E/e'	11.22 $\pm$ 5.74	7.56 $\pm$ 2.14	0.004
Left atrial vol/BSA	29.31 $\pm$ 7.21	29.44 $\pm$ 4.96	0.94
LV GLS	18.10 $\pm$ 2.97	19.74 $\pm$ 2.36	0.03
TAPSE	23.2 $\pm$ 4.62	23.6 $\pm$ 4.05	0.73
S' right ventricle	9.89 $\pm$ 3.17	9.13 $\pm$ 2.63	0.34
Strain of right ventricle	-21.5 $\pm$ 2.25	-21.48 $\pm$ 2.9	0.9
Asymptomatic atherosclerosis	49%	20%	0.027
Carotid PWV	8.58 $\pm$ 2.51	6.94 $\pm$ 1.12	0.004

Values in italics are significant values.

2. In patients treated with dasatinib ($n = 9$) two pleural effusion occurred;
3. In patients treated with ponatinib ($n = 3$) no events occurred.

New-onset arterial hypertension was found in 6.6% ($n = 2$) of patients (1 patient treated with nilotinib and 1 with dasatinib) (Table 3).

In regard to group B, cardiovascular events were registered in 16% ($n = 4$) of patients: 1 had CAD (4%), 2 had DVT (8%), while 1 had pleural effusion (4%). New-onset arterial hypertension was reported in 1 (4%) of the patients (Table 3).

Cardiovascular adverse events were more frequent among patients treated with new TKIs compared to patients treated with imatinib (30 vs. 16%, *p* value: 0.044). Due to the small sample size, it was not possible to compare each treatment group. However, it was evident that most of the adverse events occurred in the nilotinib group.

Fig. 1. Correlation between age and GLS reduction in the two groups.

An analysis of the echocardiographic measurements did not show significant differences between the two groups in regard to the LVEF and systolic parameters which were obtained through tissue Doppler imaging of the mitral annulus. However, significant differences were observed by assessing myocardial deformation indices. Left ventricular GLS was significantly reduced in group A when compared to group B (-18.10 ± 2.97 vs. $19.74 \pm 2.36\%$, p value: 0.03). As for diastolic function, the septal e' wave was reduced in group A when compared to group B (9.14 ± 1.4 vs. 7.66 ± 3.02 , p value: 0.03), while the E/e' ratio was increased in group A (11.22 ± 5.74 vs. 7.56 ± 2.14 , p value: 0.004). Right ventricular functional parameters did not change significantly among the two groups (see Table 4 for echocardiographic parameters).

We also evaluated the impact of each drug on cardiac function, even if the small sample size did not allow a statistically significant comparison among individual groups. However, it seems that patients treated with nilotinib and ponatinib had lower GLS values compared to patients treated with imatinib and dasatinib (Fig. 1).

A significantly higher incidence of preclinical carotid atherosclerosis was reported in patients from group A compared to group B ($p = 0.027$). Arterial stiffness significantly increased in group A compared to group B ($p = 0.004$). Data is reported in Table 4. Stiffness values, when comparing each treatment group, tended towards a deterioration in patients treated with nilotinib and ponatinib.

Discussion

There has already been some evidence to suggest that new TKIs could have toxic effects on the cardiovascular system [11–14]. In line with this evidence, our study showed an increased incidence of arterial thrombotic events in patients treated with new-generation TKIs (group A) compared to first-generation molecules (group B). The prevalence of thrombotic events tended to be higher in the group treated with nilotinib when compared with imatinib; the group of patients treated with ponatinib was too small to enable us to draw any conclusions. Indeed, nilotinib and ponatinib could influence an accelerated progression of atherosclerosis with or without the presence of concurrent cardiovascular risk factors [15].

The pathophysiology of ischemic events, such as PAD and accelerated atherosclerosis, is attributed to the inhibition of Src, KIT, and PDGFR. These kinases are important for the regulation of vascular tone, endothelial function, and the release of antithrombotic substances (t-PA, heparin).

Certainly, the presence of more cardiovascular risk factors in group A in addition to second-generation TKIs contributed to increase the risk of cardiovascular events in this group. It is known in the literature that patients treated with nilotinib and ponatinib had a major risk of cardiovascular events if they had cardiovascular risk factors and a high to very high SCORE risk (Systematic Coronary Risk Evaluation). Caocci et al. [16] demonstrated that patients treated with ponatinib and with a high to very high SCORE risk showed a significantly higher incidence rate of arterial occlusive events. In patients treated with ponatinib, the SCORE risk was confirmed as a significant predictive factor.

In addition, these authors demonstrated that patients aged ≥ 60 years who were treated with aspirin had a lower incidence rate of arterial occlusive events. Thus, they emphasize personalized prevention strategies based on cardiovascular risk factors, i.e. prophylaxis with 100 mg/day of aspirin in patients aged ≥ 60 years treated with ponatinib. There were no significant differences between the two groups regarding the occurrence of arterial hypertension during treatment. Indeed, new- and old-generation TKIs, excluding ponatinib, rarely determined new onset of hypertension [17].

In accordance with data from the literature, a low incidence of pleural effusion was observed in patients receiving dasatinib. Dasatinib is a multikinase inhibitor. It inhibits the following kinases: BCR-ABL, SRC family (SRC, LCK, YES, FYN), c-KIT, EPHA2, and PDGFR beta.

Especially SRC and PDGFR are involved in cellular proliferation mechanisms and vascular tone regulation. The pathophysiology of pleural effusion, usually associated with the drug, is not completely known; in addition to its autoimmunity mechanism, it probably has a role in the inhibition of both the above-mentioned kinases [18]. The proliferation of smooth-muscle cells could be decisive in the development of pulmonary hypertension during treatment. In this study we did not observe pulmonary hypertension in the population. The echocardiographic assessment showed a normal ejection fraction in the whole population with no significant differences among the two groups. LVEF is not a sensitive parameter because it is modified after myocardial damage occurs. The tissue Doppler may detect the deterioration of the longitudinal systolic function; however, it is less sensitive and accurate than myocardial deformation indices. In this study, it did not show significant differences between the two groups. Myocardial deformation indices of left ventricle (GLS) are known to be a very sensitive tool for the early detection of left ventricular dysfunction, and they have many advantages [19].

Several studies demonstrated that GLS is a predictor of cardiotoxicity. Particularly, the strongest predictor of cardiac dysfunction after chemotherapy was GLS variation measured during follow-up. A reduction of GLS of 8% compared with baseline appears not to be clinically meaningful, whereas a GLS reduction >15% is very likely to be of clinical significance. Thus, GLS variation should be monitored during anticancer treatment; absolute GLS reduction can also be predictive of cardiovascular events [20].

In our study, GLS values were significantly reduced in group A compared to group B. By analyzing GLS in each treatment group, we observed lower values in the nilotinib-treated patients compared to those treated with dasatinib and imatinib. However, we are aware that the size of our sample is too small to draw any definite conclusions. Therefore, the idea that the first two drugs have a greater cardiotoxic effect is only speculation and cannot be proved.

Few studies in the literature have showed an increase of arterial stiffness in patients treated with drugs targeting VEGF, but very little is known about the effects caused by other TKIs [21]. In our study, PWV was found to be significantly increased in patients treated with new-generation TKIs compared to the group treated with imatinib. Again, patients treated with nilotinib had stiffer arteries than those treated with dasatinib or imatinib. The influence of cardiovascular risk factors, especially arterial hy-

pertension, in determining the alteration of arterial stiffness, cannot be excluded. Therefore, they should be properly addressed before starting the treatment.

Despite being more effective, new-generation TKIs, especially nilotinib, are burdened by major cardiovascular toxicity. The prevailing type of cardiovascular toxicity appears to be vascular, leading to ischemic and thrombotic events (PAD, CAD, DVT, preclinical atherosclerosis). Subclinical left ventricular dysfunction, which was shown by a reduction of GLS, can also occur in these patients. However, imatinib seems to be safer in terms of long-term cardiovascular toxicity. According to the literature, it is also able to reduce glycemic values and pulmonary hypertension [22].

We are aware that the present study has many limitations, in particular the small sample size, the heterogeneity of the study population, and the inclusion of both GIST and CML patients that could have affected the results. However, the purpose of the present study was to assess the cardiotoxic profile of TKIs independently from the type of tumor for which the drug was administered. It is worth noting that patients treated with ponatinib and some patients treated with nilotinib and dasatinib have previously been treated with another TKI. This could have made them more prone to developing cardiotoxic events. On the other hand, we are also aware that this represents real clinical practice and as such should be taken into consideration when starting treatment with these drugs.

Another limitation of the study is its retrospective structure and thus the inhomogeneous timing of the cardiological evaluation during treatment. However, in this regard, it is worth noting that the duration of treatment and the exposure to the potential cardiotoxic effect of the drugs in patients from group A was shorter than those in group B. This evidence reinforces the idea that there is a higher potential risk burden connected to the latest generation of TKI drugs. Regarding the retrospective structure of the study, it is possible to highlight another limitation, the lack of a complete baseline dataset. All patients had a normal baseline ejection fraction as an inclusion criterion and absence of previous cardiovascular events. However, we did not have the baseline measurement of GLS and PWV.

Nevertheless, based on our knowledge, this is the first study that highlights cardiovascular toxicity of TKIs targeting BCR-ABL, by measuring GLS and arterial stiffness and as such it increases our knowledge of this class of drugs. Its advantage has been its ability to show what can happen in the real-world clinical practice. However, to

confirm the hypothesis of a cardiotoxic burden caused by the latest-generation TKI, wider and prospective studies, including a homogeneous population, are necessary.

Conclusions

Our study confirmed that imatinib is a relatively safe drug and it reveals that latest-generation TKIs may have a burden of cardiovascular complications. Moreover, it revealed that early signs of cardiac and vascular damage can be detected in such patients by measuring GLS and arterial stiffness before they become apparent.

Given the burden of cardiovascular toxicity associated with TKI treatment, it is advisable to perform a careful cardiovascular examination of patients before starting this treatment. Cardiovascular risk factors should be carefully addressed and medical therapy should be optimized. Patients considered at risk should be monitored during treatment with an echocardiography, possibly including GLS measurement, an ultrasound scan of the carotid arteries, and an arterial stiffness evaluation. Several studies, in fact, have already showed the importance of an early detection of cardiovascular damage to improve the prognosis of patients treated with chemotherapy by using cardioprotective therapy [23–26](Fig. 1).

Study Limitations

Our study has many limitations: a small sample size and the absence of a baseline cardiac evaluation of the patients. The sample size is small because the study reflects the experience of a single center and is not a multicentric study. It is known that CML and GIST have a low incidence. Certainly in the future, the sample size will have to be expanded for greater statistical significance.

The absence of baseline cardiac evaluation with myocardial deformation indices and arterial stiffness evaluation is another limitation of the study but it reflects the lack of attention given to cardio-oncology in the past. In fact, only for a few years considering the cardiotoxic ef-

fects of TKIs, all centers subjected patients to basal cardiology evaluation and during follow-up, to monitoring and treating cardiovascular risk factors. In our study, we assessed patients years after starting treatment, and we do not have echocardiographic data before starting treatment.

Statement of Ethics

Ethics approval was not necessary because patients have been subjected to routine clinical and instrumental evaluation (diagnostic and therapeutic assessment on the basis of current ESC Guidelines). The Ethics Committee of the Policlinico “P. Giaccone” Palermo gave their agreement.

All patients enrolled signed informed consent to participate in the study. All data about the patients are anonymous.

Disclosure Statement

All authors have not conflicts of interest to declare.

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Author Contributions

D. Di Lisi, G. Novo, and S. Novo performed the cardiological examination and were major contributors in writing the manuscript.

F. Macaione and E. Bronte analyzed and interpreted the data.

V. Accurso, G. Badalamenti, G. Rinaldi, S. Siragusa, and A. Russo contributed by recruiting patients and writing the manuscript.

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