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Cardiotoxicity Associated with Tyrosine Kinase Inhibitors in Philadelphia Chromosome-Positive Leukemias: An Overview of Mechanisms, Clinical Implications, and Management Strategies

Rashmi H.R.[1,*], Kishan A.[2], Sunitha M.[3], Ganesh N.S.[4]

Abstract

Tyrosine kinase inhibitors have greatly enhanced the outlook for individuals diagnosed with Philadelphia chromosome-positive leukemias, including chronic myeloid leukemia and acute lymphoblastic leukemia. However, these therapeutic agents are associated with Cardiotoxicities and can manifest as left ventricular dysfunction, which may progress to heart failure, along with electrocardiographic abnormalities, dysrhythmias, hypertension, myocardial ischemia, and thromboembolic events. The unclear frequency of drug-induced cardiovascular complications, coupled with uncertainties regarding their reversibility and long-term safety, highlights the need for a multidisciplinary approach. This initiative should include collaboration among cardio-oncology specialists, primary care physicians, pharmacologists, and toxicologists. In this context, we focus on the cardiovascular events linked to targeted anticancer therapies by providing a brief overview of the mechanisms behind cardiotoxicity and offering clinical guidance for effective patient management. Cardiotoxicity is a notable concern in the treatment of Ph+ leukemia with Tyrosine kinase inhibitors. Vigilant cardiovascular monitoring, including baseline and periodic assessment of cardiac function, is crucial for early detection and management of cardiotoxic effects. Strategies to mitigate cardiotoxicity include optimizing cardiovascular risk factors and timely therapeutic interventions upon signs of cardiac dysfunction.

Keywords: Tyrosine kinase inhibitors (TKIs), chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL), cardio-oncology, drug-induced cardiovascular complications, cardiovascular monitoring

***Author for Correspondence**
Rashmi H.R.
E-mail: rashmihr36@gmail.com

[1,2]Student, Department of Pharmaceutics, T. John College of Pharmacy, Bengaluru, India
[3]Assistant Professor, Department of Pharmaceutics, T. John College of Pharmacy, Bengaluru, India
[4]Professor and Head, Department of Pharmaceutics, T. John College of Pharmacy, Bengaluru, India

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INTRODUCTION

Philadelphia-positive (Ph+) leukemia refers to leukemias that contain the Philadelphia chromosome, a distinct genetic abnormality caused by a translocation between chromosomes 9 and 22. This translocation results in the formation of a fusion gene known as BCR-ABL1, which encodes an abnormal tyrosine kinase protein that drives the uncontrolled proliferation of leukemic cells. The two main types of Ph+ leukemias are chronic myeloid leukemia (CML) and a subset of acute lymphoblastic leukemia (ALL) [1–7].

TKIs are targeted therapies designed to inhibit the BCR-ABL1 tyrosine kinase, thus controlling the growth of leukemic cells. Key TKIs include:

Imatinib. The first TKI was approved for CML and Ph+ ALL, significantly improving survival rates. Dasatinib and Nilotinib Second-generation TKIs, are used when resistance or intolerance to imatinib occurs. Bosutinib and Ponatinib are further options for patients with resistance or specific mutations [8].

Cardiotoxicity has become an emerging concern with tyrosine kinase inhibitors (TKIs) based chemotherapy, which are crucial in targeting various cancers, and often have unintended effects on the cardiovascular system this TKIs have non-specific targeting.

- Tyrosine kinases are enzymes that regulate many cellular processes, including those in the heart and blood vessels. TKIs are designed to block the signaling pathways driving cancer growth, but they can also interfere with normal cardiovascular signaling, leading to unintended side effects.
- Many TKIs target pathways (e.g., VEGF, PDGF, and HER2) that are also important in the cardiovascular system. For example, blocking VEGF (vascular endothelial growth factor) can impair angiogenesis and cause hypertension, thrombosis, or heart failure.
- VEGF inhibitors (e.g., sunitinib, sorafenib) reduce the production of nitric oxide, a vasodilator, leading to vasoconstriction and increased blood pressure. Chronic hypertension, if unmanaged, can contribute to long-term cardiovascular complications [4, 6].

METHODOLOGY

To conduct this review, a comprehensive literature search was performed using databases, such as PubMed, Embase, and Google Scholar. The search included articles published between [2008] and [2023], focusing on studies that investigated the cardiotoxic effects of TKIs in Philadelphia chromosome-positive (Ph+) leukemia patients. Keywords used in the search included "cardiotoxicity," "tyrosine kinase inhibitors," "Philadelphia chromosome," "chronic myeloid leukemia," "acute lymphoblastic leukemia," "imatinib," "dasatinib," and "nilotinib." We included clinical trials, observational studies, case reports, and review articles that provided relevant data on the cardiovascular outcomes associated with TKI therapy. Studies were selected based on predefined inclusion criteria: those assessing cardiotoxicity in Ph+ leukemia patients and reporting clinical or mechanistic insights. Exclusion criteria included studies on non-Ph+ leukemia patients, articles with insufficient data, or studies not related to cardiotoxicity. Data extraction was carried out systematically, capturing information on study design, patient population, type of TKI used, cardiotoxicity manifestations, and outcomes. Results were analyzed to identify common patterns of cardiotoxicity across different TKIs and their potential mechanisms.

DISCUSSION

The use of TKIs in leukemia patients is a topic of considerable debate among clinicians and researchers. While TKIs have been prescribed for managing various leukemia patients in various patient populations.Its specific role and safety in heart failure remains uncertain.

In the last 20 years, TKIs have transformed cancer treatment, leading to notable improvements in outcomes for several types of cancers, including CML, ALL, gastrointestinal stromal tumors, and more. Despite their efficacy and relatively safer profiles compared to traditional chemotherapy.

This discussion section aims to address a key comprehensive analysis of the current knowledge surrounding TKIs use in heart failure.

TKIs can lead to cardiotoxicity through various mechanisms, including [9–12].

- *Off-target inhibition:* TKIs (Table 1) are designed to inhibit the BCR-ABL tyrosine kinase, but they can also affect other kinases involved in cardiac function.
- *Oxidative stress:* Some TKIs induce oxidative stress in cardiac cells, leading to damage and dysfunction.

- *Endothelial dysfunction:* TKIs can impair the function of endothelial cells, contributing to vascular complications.
- *Direct myocardial damage:* Some TKIs have been associated with direct toxic effects on cardiac myocytes.

Table 1. Summary of TKIs and associated cardiac abnormalities.

Drug	**Molecular Target**	**Therapeutic Indication**	**Cardiac Abnormalities**	**Advice**
Imatinib	ABL1/2, PDGFRa/b, c-KIT, hERG	CML, Ph? B-ALL, CMML, CEL, GIST	Fluid retention Palpitation, pulmonary edema, MI, pericardial effusion angina pectories, atrial fibrillation.	Electrocardiogram (ECG) monitoring at regular intervals (before and during treatment) and attention to electrolyte imbalance (especially hypokalemia and hypomagnesemia) Caution when administering CYP3A4 inhibitors (e.g., ketoconazole, rifampicin, and grapefruit juice).
Dasatinib	ABL1/2, PDGFRa/b, c-KIT, NRTK (Src family), hERG	Resistant CML and Ph? B-ALL	QT prolongation, fluid retention, pulmonary arterial hypertension, CHF arrhythmia(including tachycardia), palpitations MI, cor pulmonale.	Due to the risk of pulmonary arterial hypertension with dasatinib: close monitoring for signs or symptoms of cardiac disease; consider echocardiographical evaluation in case of pre-existing risk factors and drug withdrawal/dose reduction.
Nilotinib	ABL1/2, PDGFRa/b, c-KIT, hERG	Resistant CML	QT prolongation and, A-V block cardiac fluttering, pericardial effusion coronary disease, cyanosis, decrease LVEF.	–
Sunitinib	VEGFR1/2/, c-KIT, PDGFRa/b, RET, CSF-1R, FLT3, hERG	MRCC, resistant GIST, NETs	MRCC, resistant GIST, NETs, torsades de pointes, cardiomyopathy, pericardial effusion.	–
Bosutinib	BCR-ABL, Src, Lyn and Hck, PDGF, c-KIT	CML Ph-positive newly diagnosed in a chronic phase or after prior TKI in a chronic/blast phase	QTc prolongation. Fluid retention.	–

Cardiotoxicity can Present in Several Ways

- *Heart failure:* Reduced left ventricular ejection fraction (LVEF) and symptomatic heart failure have been reported [13–16].
- *Arrhythmias:* QT prolongation and other arrhythmias may develop, potentially resulting in serious cardiac complications**.**
- *Hypertension:* High blood pressure is a frequent side effect that can worsen other cardiovascular risks.
- *Vascular events:* There is an observed increased risk of arterial thrombosis, including heart attacks and strokes.

The cardiovascular safety of each TKI must be evaluated individually. In the following section, we will examine the cardiovascular safety profiles of various TKIs used to treat CML and ALL.

Imatinib

It typically has a lower incidence of cardiotoxicity compared to second and third-generation TKIs. In 2006, Kerkelä et al. reported a case series involving 10 patients, along with in vitro and animal studies, suggesting that imatinib might cause cardiotoxic effects. However, subsequent clinical trials that followed many patients over an extended period did not demonstrate an increased risk of cardiovascular events (CVEs) or cardiotoxicity. There is also a possibility that imatinib may have beneficial metabolic and vascular effects. It has been reported to reduce blood glucose levels and prevent the formation of atherosclerotic lesions in the aorta of diabetic mice [17–19].

Dasatinib

Dasatinib is effective against many imatinib-resistant forms of BCR-ABL and demonstrates approximately 325 times greater potency than imatinib in inhibiting BCR-ABL. It also targets several other kinases, including members of the Src family. Dasatinib has been approved for first-line therapy for CML due to its superior complete cytogenetic response rates at 12 months compared to imatinib. However, it is associated with an increased risk of pulmonary arterial hypertension and pleural effusion in 28% of patients, which can indirectly impact cardiac function [20].

Nilotinib

This drug is associated with an increased risk of vascular events, including peripheral arterial occlusive disease. It has also been linked to changes in ECGs and peripheral arterial disease. During the Phase I clinical trial of nilotinib, ECGs showed a prolongation of the corrected QT interval by 5–15 ms in a subgroup of patients. However, in the ENESTnd trial, patients were closely monitored, and none developed a corrected QT interval exceeding 500 ms. Additionally, no cases of torsades de pointes or malignant arrhythmias were reported after long-term follow-up [21].

Bosutinib and Ponatinib

Both have been linked to a higher incidence of CVEs, especially ponatinib, which carries a significant risk of arterial thrombosis and cardiomyopathy. Ponatinib can cause myocardial infarction by inhibiting the AKT signaling pathway, inhibiting ERK, and inducing apoptosis. Compared to dasatinib and nilotinib, severe congestive heart failure and left ventricular dysfunction are less common but more noticeable with imatinib treatment, particularly in patients on higher doses (over 600 mg/day). In contrast, prolongation of QT interval is relatively frequent among patients treated with either dasatinib or nilotinib. This highlights the overall advantages of TKI therapy while underscoring the need for careful monitoring, particularly in older patients.

Anticancer-induced cardiotoxicity represents a rapidly evolving field with clinical implications for primary care physicians who play a pivotal role in managing practical issues, such as hypertension. This review aims to address emerging CVEs associated with targeted anticancer drugs, focusing on left ventricular dysfunction/heart failure, hypertension, and thromboembolism, which are critical interrelated aspects in the oncological setting.

Despite its widespread use, LVEF is not a perfect measure for assessing cardiac functional reserve. Due to the subjective nature of interpreting LVEF via echocardiography (ECHO), a decrease in this measure does not always indicate cardiac damage. Conversely, a stable LVEF should not be interpreted as proof of the absence of cardiotoxicity. Additionally, there are varying methods for monitoring LVEF in clinical trials (e.g., a single drop in LVEF versus a decline of at least 10% points from the baseline). Given the ambiguous evidence from clinical practice, it may be beneficial to return to basic science to better understand the mechanisms of cardiotoxicity.

Adverse events (AEs) in oncology trials are documented using the Common Terminology Criteria for Adverse Events (CTCAE), which differ from the outcomes measured in cardiology trials [22].

MONITORING AND MANAGEMENT

Given the potential for cardiotoxicity, proactive monitoring and management are crucial.

Baseline Assessment

Cardiac evaluation, including ECG and ECHO, should be performed before initiating TKI therapy.

ECG Monitoring

It is prudent to suggest performing an ECG before starting any TKI therapy, as most TKIs can influence the QT interval, and there is significant individual variability in QTc changes. If the QTc prolongation reaches 440 ms or if ponatinib is being administered, more frequent monitoring is advised. This should continue at 3–6-month intervals if there is a prolongation of 30 ms or more from the baseline [23].

Regular Monitoring

Regular monitoring of cardiac function and blood pressure is advised throughout the treatment.

Risk Factor Modification

Managing modifiable cardiovascular risk factors, such as hypertension, diabetes, and hyperlipidemia, is crucial. Regarding diabetes management, standard recommendations apply to patients who develop diabetes while on TKI treatment, with particular emphasis on those receiving nilotinib. It is noteworthy that patients with diabetes who were treated with nilotinib as a first-line option frequently experienced hyperglycemia, with around half of these cases classified as grade 3–4. However, no significant diabetes-related complications (such as hyperosmolar coma, ketoacidosis, or hospitalizations) were reported, and 74% of patients did not require changes to their antidiabetic medications [24].

Dose Adjustment and Drug Switching

In instances of substantial cardiotoxicity, it may be necessary to adjust the dosage or switch to a different TKI that has a different toxicity profile.

Multidisciplinary Approach

Collaboration between oncologists, cardiologists, and other healthcare providers is vital to optimize patient outcomes.

CONCLUSIONS

While TKIs have revolutionized the treatment of Ph+ leukemias, and significantly improved the prognosis, their potential for cardiotoxicity requires careful consideration. Second- and third-generation anti-BCR-ABL TKIs (especially nilotinib and ponatinib) cause vascular toxicity, such as arterial thrombosis (myocardial infarction, peripheral arterial occlusive disease, cerebrovascular events) with several mechanisms, such as regular cardiac monitoring, proactive management of cardiovascular risk factors, personalized treatment strategies, and a multidisciplinary approach, healthcare providers can minimize the impact of cardiotoxicity and ensure the best possible outcomes for patients. Despite significant advancements in the use of TKIs for Ph+ leukemia, several gaps remain in optimizing patient outcomes, particularly in minimizing cardiotoxicity. Future research should focus on identifying specific biomarkers that can predict cardiotoxicity in patients receiving TKIs, allowing for personalized treatment approaches. Furthermore, additional long-term studies are required to assess the cumulative cardiac effects of extended TKI therapy, particularly in patients who have pre-existing cardiovascular conditions. Exploring novel cardioprotective agents or strategies that can be co-administered with TKIs may improve tolerability and reduce cardiac side effects without compromising therapeutic efficacy. Furthermore, the development of next-generation TKIs with more selective kinase inhibition profiles could reduce off-target effects, including cardiotoxicity. Research should also prioritize better risk stratification tools and guidelines for monitoring cardiac function in these patients, ensuring early detection and management of cardiovascular complications. Ultimately, integrating these insights could lead to more personalized and safer TKI-based treatments, enhancing both survival rates and quality of life for Ph+ leukemia patients.

REFERENCES

1. Berisha A, Placci A, Piccaluga PP. Cardiovascular toxicity of targeted therapies in hematologic malignancies. Hemato. 2023;4(1):68–75. doi:10.3390/hemato4010007.
2. Berisha A, Placci A, Piccaluga PP. Cardiovascular toxicity of targeted therapies in hematologic malignancies. Hemato. 2023. doi:10.3390/hemato4010007. Corpus ID: 257263317.
3. Manouchehri A, Kanu E, Mauro MJ, Aday AW, Lindner JR, Moslehi J. Cardiovascular effects of tyrosine kinase inhibitors in chronic myeloid leukemia. Arterioscler Thromb Vasc Biol. 2020;40:301–8.. doi:10.1161/ATVBAHA.119.313353.
4. Raschi E, De Ponti F. Cardiovascular toxicity of anticancer-targeted therapy: emerging issues in the era of cardio-oncology. Intern Emerg Med. 2011;7(2):113–31. doi:10.1007/s11739-011-0774-Y.
5. Novo G, Di Lisi D, Fiuza M, Pinto FJ. Cardiovascular damage induced by anti-BCR-ABL tyrosine kinase inhibitors. In: Current Clinical Pathology. Cham: Springer International Publishing; 2019. pp. 45–55. doi:10.1007/978-3-319-93402-0_6.
6. Grela-Wojewoda A, Pacholczak-Madej R, Adamczyk A, Korman M, Püsküllüoğlu M. Cardiotoxicity induced by protein kinase inhibitors in patients with cancer. Int J Mol Sci. 2022;23(5):2815. doi:10.3390/ijms23052815.
7. Steegmann JL, Baccarani M, Breccia M, Casado LF, García-Gutiérrez V, Hochhaus A, et al. European LeukemiaNet recommendations for the management and avoidance of adverse events of treatment in chronic myeloid leukemia. Leukemia. 2016;30(8):1648–71. doi:10.1038/leu.2016.104.
8. Moslehi JJ, Deininger M. Tyrosine kinase inhibitor-associated cardiovascular toxicity in chronic myeloid leukemia. J Clin Oncol. 2015;33(35):4210–8. doi:10.1200/JCO.2015.62.4718.
9. Schiffer CA. BCR-ABL tyrosine kinase inhibitors for chronic myelogenous leukemia. N Engl J Med. 2007;357:258–65.
10. Gustafson D, Fish JE, Lipton JH, Aghel N. Mechanisms of cardiovascular toxicity of BCR-ABL1 tyrosine kinase inhibitors in chronic myelogenous leukemia. Curr Hematol Malig Rep. 2020;15(1):20–30. doi:10.1007/s11899-020-00560-x.
11. Marcolino MS, Ribeiro AL, Clementino NCD, Barbosa MM, et al. The use of imatinib mesylate has no adverse effects on heart function: results of a pilot study in patients with chronic myeloid leukemia. Leuk Res. 2011;35(3):317–22. doi:10.1016/j.leukres.2010.07.011.
12. Grela-Wojewoda A, Pacholczak-Madej R, Adamczyk A, Korman M, Püsküllüoğlu M. Cardiotoxicity induced by protein kinase inhibitors in patients with cancer. Int J Mol Sci. 2022;23(5):2815. doi:10.3390/ijms23052815.
13. Cirmi S, El Abd A, Letinier L, Navarra M, Salvo F. Cardiovascular toxicity of tyrosine kinase inhibitors used in chronic myeloid leukemia: an analysis of the FDA adverse event reporting system database (FAERS). Cancers (Basel). 2020;12(4):826. doi:10.3390/cancers12040826.
14. Xu Z, Cang S, Yang T, Liu D. Cardiotoxicity of tyrosine kinase inhibitors in chronic myelogenous leukemia therapy. Hematol Rev. 2009;1(1):e4 doi:10.4081/hr.2009.e4.
15. Sayegh N, Yirerong J, Agarwal N, Addison D, Fradley M, Cortes J, et al. Cardiovascular toxicities associated with tyrosine kinase inhibitors. Curr Cardiol Rep. 2023;25(4):269–80. doi:10.1007/s11886-023-01845-2.
16. Samra B, Kantarjian HM, Sasaki K, Alotaibi AS, Konopleva M, O'Brien S, et al. Discontinuation of maintenance tyrosine kinase inhibitors in Philadelphia chromosome-positive acute lymphoblastic leukemia outside of transplant. Acta Haematol. 2021;144(3):285–92. doi:10.1159/000510112.
17. Chaar M, Kamta J, Ait-Oudhia S. Mechanisms, monitoring, and management of tyrosine kinase inhibitor-associated cardiovascular toxicities. Onco Targets Ther. 2018;11:6227–37. doi:10.2147/OTT.S170138.
18. Kantarjian HM, Giles F, Gattermann N, Bhalla K, Alimena G, Palandri F, et al. Nilotinib (formerly AMN107). Blood. 2007;110(10):3540–6. doi:10.1182/blood-2007-03-080689.
19. Shamroe CL, Comeau JM. Ponatinib: a new tyrosine kinase inhibitor for the treatment of chronic myeloid leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia. Ann Pharmacother. 2013;47(11):1540–6. doi:10.1177/1060028013501144.

20. Li YF, Combes FP, Hoch M, Lorenzo S, Sy SKB, Ho YY. Population pharmacokinetics of asciminib in tyrosine kinase inhibitor-treated patients with Philadelphia chromosome-positive chronic myeloid leukemia in chronic and acute phases. Clin Pharmacokinet. 2022;61(10):1393–1403. doi:10.1007/s40262-022-01148-9. Erratum in: Clin Pharmacokinet. 2022;61(10):1475–6. doi:10.1007/s40262-022-01166-7.
21. Jabbour E, Deininger M, Hochhaus A. Management of adverse events associated with tyrosine kinase inhibitors in the treatment of chronic myeloid leukemia. Leukemia. 2011;25:201–10. doi:10.1038/leu.2010.215.
22. Grela-Wojewoda A, Pacholczak-Madej R, Adamczyk A, Korman M, Püsküllüoğlu M. Cardiotoxicity induced by protein kinase inhibitors in patients with cancer. Int J Mol Sci. 2022;23(5):2815. doi:10.3390/ijms23052815.
23. Mikami T, Kato I, Oiki N, Okamoto S, Kamitori T, Tasaka K, et al. A rare case of relapsed pediatric acute lymphoblastic leukemia after hematopoietic stem cell transplantation. J Pediatr Hematol Oncol. 2022;44(2). doi:10.1097/MPH.0000000000002157.
24. Kantarjian H, Cortes J. Considerations in the management of patients with Philadelphia chromosome-positive chronic myeloid leukemia receiving tyrosine kinase inhibitor therapy. J Clin Oncol. 2011;29(12):1512–6. doi:10.1200/JCO.2010.33.9176.