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Cardiotoxicity of the BCR-ABL1 tyrosine kinase inhibitors: emphasis on ponatinib

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Abstract

The advent of tyrosine kinase inhibitors (TKIs) targeted therapy revolutionized the treatment of chronic myeloid leukemia (CML) patients. However, cardiotoxicity associated with these targeted therapies puts the cancer survivors at higher risk. Ponatinib is a third-generation TKI for the treatment of CML patients having gatekeeper mutation T315I, which is resistant to the first and second generation of TKIs, namely, imatinib, nilotinib, dasatinib, and bosutinib. Multiple unbiased screening from our lab and others have identified ponatinib as most cardiotoxic FDA approved TKI among the entire FDA approved TKI family (total 50+). Indeed, ponatinib is the only treatment option for CML patients with T315I mutation. This review focusses on the cardiovascular risks and mechanism/s associated with CML TKIs with a particular focus on ponatinib cardiotoxicity. We have summarized our recent findings with transgenic zebrafish line harboring BNP luciferase activity to demonstrate the cardiotoxic potential of ponatinib. Additionally, we will review the recent discoveries reported by our and other laboratories that ponatinib primarily exerts its cardiotoxicity via an off-target effect on cardiomyocyte prosurvival signaling pathways, AKT and ERK. Finally, we will shed light on future directions for minimizing the adverse sequelae associated with CML-TKIs.

Keywords

Ponatinib; Tyrosine kinase inhibitor; Cardiotoxicity; Cardio-oncology

Introduction:

Over the past 30 years, the care of cancer patients has advanced [1, 2]. On the contrary, many agents in anticancer drugs have cardiotoxic manifestations due to which a significant percentage of cancer patients are suffering from adverse effects of cancer therapeutics. Patients with pre-existing cardiovascular disorders are at higher risk of drug-induced

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CONFLICT OF INTERESTS

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cardiotoxicity. Therefore, there is a desperate need for strategies to identify and overcome cardiotoxicity during cancer therapy. This recognition has culminated in the inception of a multidisciplinary field: known as cardio-oncology. The primary goals of the rapidly growing discipline of cardio-oncology are to better understand the pathophysiology of cancer therapy-associated cardiotoxicity and to provide early prediction, detection, management, and treatment of cardiac complications in patients with, or who survive cancer. Importantly, the majority of CML patients have to live with cancer and requires daily medication. Only a few CML patients can approach to stop TKI treatment and maintain a state of “treatment-free remission” (TFR). Only this small fraction of CML patients fall in the category of “cancer survivors.” This need for a lifelong treatment further enhances the probabilities of drug-induced toxicity. An obstruction in the field has been the lack of an appropriate model system to perform preclinical studies for accurate prediction of cardiotoxicity in humans [3]. Extensive efforts have been made to understand the mechanism of chemotherapy-induced cardiomyopathy, and maximum information was derived from anthracyclines. However, the frequency of molecular targeted therapies-induced cardiotoxicity is largely unknown and potentially underestimated.

Targeted therapies are highly effective in the treatment of cancer and have significantly improved the life expectancy of cancer patients. Chronic myeloid leukemia (CML) signifies a remarkable success story in the era of targeted therapy. CML affects 1-2 out of every 100,000 adults. The disease represents 15% of new cases of leukemia in adults. An estimated 60,530 new cases of leukemia will be diagnosed in the US in 2020 [4]. CML is associated with the reciprocal translocation between chromosomes 9 and 22 (t(9;22) or Philadelphia (Ph) chromosome resulting in the breakpoint cluster region-Abelson (*BCR-ABL1*) fusion gene [5, 6]. This oncoprotein is a continuously produced active tyrosine kinase which promotes growth via downstream signaling pathways, for example, RAS, RAF, MYC, and STAT.

The constitutive activity of the oncogenic BCR-ABL1 tyrosine kinase is the primary cause of CML progression and, thus, serves as an ideal molecule for targeted therapy [7–11]. Numerous TKIs, including imatinib, nilotinib, dasatinib, bosutinib, and ponatinib, have targeted this kinase.

Undeniably, targeted inhibition of BCR-ABL1 with TKIs has led to an improvement in the survivorship of patients diagnosed with CML. Unfortunately, these TKIs are also lead to unwanted adverse cardiovascular effects (Table 1). Notably, several recent reports have suggested that ponatinib is the most cardiotoxic agent in all FDA approved TKIs ([12, 13]. Since there is no alternative treatment option for CML patients with the T315I mutation, at present, the only hope is to better understand the molecular mechanism of ponatinib-induced cardiotoxicity and develop strategies to prevent/treat adverse effect. Herein, we focused on discussing the ponatinib associated cardiotoxic effects, current understanding of the molecular mechanism.

Tyrosine kinase inhibitors for CML treatment

Imatinib:

In 2003, imatinib became the first FDA approved TKI to manage CML [14]. Imatinib function by binding to the BCR-ABL1 kinase domain, located in an inactive conformation in a pocket reserved for the ATP binding site. The phase III IRIS study reported an unprecedented total cytogenetic response rate of approximately 86% in CML-CP. However, due to drug resistance, some patients relapsed. Imatinib was generally well-tolerated, and it has a long-term safety profile. The imatinib associated adverse cardiac effects are depicted in table 1.

The development of point mutations in tyrosine kinase domain, which prevents efficient imatinib binding to the target, was the primary factor in developing imatinib resistance [15]. Till date, more than 100 mutations have been identified, which promotes genomic instability and contributes to imatinib resistance [7, 16–20]. Shortly after the development of imatinib-resistance, second and third-generation tyrosine kinase inhibitors were designed to treat CML [21–24]. The first well-known imatinib resistance mutation leads to an exchange of threonine at position 315 to isoleucine (T315I). At present, BCR-ABL-T315I remains the most troublesome mutation associated with CML progression [8, 25, 26].

Dasatinib, Nilotinib, and Bosutinib

Second-generation TKIs include nilotinib, dasatinib, and bosutinib. They have a higher affinity for the binding site on the BCR-ABL1 tyrosine kinase protein. This allows for more effective inhibition of BCR-ABL1 when compared to imatinib. Dasatinib is a potent multikinase inhibitor targeting BCR-ABL1 and is effective in the treatment of patients with newly diagnosed Philadelphia-chromosome-positive (Ph+) CML in all phases of the disease. Nilotinib was approved in 2007 to treat newly diagnosed adults with CML-CP and patients with CML-CP/AP who are resistant to or intolerant of previous therapy. Bosutinib was initially approved by the FDA in 2012 and prescribed for CML patients in any phase, who are resistant or intolerant of prior TKIs. The Second-generation TKIs associated adverse cardiac effects are summarized in table 1. Although dasatinib (Sprycel, BMS-354825), nilotinib (Tasigna, AMN107), and bosutinib (Bosulif, SKI-606) were effective against imatinib-resistant CML, still patients with T315I mutation (gatekeeper mutation) suffered [27, 28].

Ponatinib

Ponatinib emerged from the need of a TKI, which is effective against the T315I mutation of the BCR-ABL1 alongside native BCR-ABL and more commonly seen mutations of BCR-ABL. The T315I mutation of the BCR-ABL1 changes the topology of the ATP binding region [44]. Residue 315 is known as the “gatekeeper” residue due to its location in front of the hydrophobic pocket. When threonine is mutated to isoleucine, the bulkier isoleucine side chain extends into the enzyme active site. The resulting steric clash blocks the entrance of a TKI into the hydrophobic pocket, but still allows access to ATP. Thus, first- and second-generation TKIs fail to inhibit BCR-ABL T315I mutation [44]. The overall structure of Ponatinib is based on the ATP-mimetic structure used in previous iterations of TKIs. The

goal in creating ponatinib was to handle the lack of an active-site hydrogen bond and the new steric hindrance caused by the isoleucine side chain [8, 45]. Ponatinib targets the T315I chain by the construction of van der Waals interaction using an ethynyl linkage.

Pre-clinical studies with ponatinib

In 2006, initial preclinical studies of ponatinib were done with *in vitro* biochemical assays. These studies were performed with K562, a BCR-ABL positive human cell line, and Ba/F3, a pro-B mouse cell line [45]. The primary purpose of these assays was to determine the ponatinib ability to inhibit BCR-ABL kinase activity and cell proliferation. The results from these experiments confirmed that ponatinib does inhibit both wild-type and mutant BCR-ABL kinase with IC₅₀ values of 0.37-2.0 nM. A dose of 40 nM has the ability to entirely suppress the development of BCR-ABL resistant mutants [45, 46]. Due to the success of *in vitro* results, ponatinib efficacy was further tested on mice models [45]. It was found that the 10 mg/kg and 30 mg/kg have the ability to suppress tumor growth, while the 50 mg/kg dose has the ability to reduce mean tumor volume by approximately 96%. The suggested dose of ponatinib is 45 mg once daily, but the label cautions that an optimal dosage has not been identified, and the majority of patients treated with ponatinib have required dose reductions to 30 or 15 mg.

Ponatinib adverse Vascular effects

Ponatinib adverse effects on the vascular system and atherosclerotic plaque formation are comparatively more recognized than the direct cardiotoxicity and recently reviewed [47–53], therefore, herein, we will only discuss in brief. In fact, ponatinib's approval was suspended in October 2013, primarily due to safety concerns arising from the increased incidence of serious vascular occlusive events. However, given that there was no alternative treatment option for CML patients with the T315I mutation, the suspension was short-lived. After a couple of months, ponatinib was reintroduced with added safety measures regarding cardiovascular risk.

The adverse vascular effect of ponatinib was clearly evident in various clinical trials. In the 5-year follow-up of the phase 2 PACE trial with 449 patients, the cumulative incidence of arterial occlusive events (AOEs), including cardiovascular, cerebrovascular, and peripheral vascular, was 26% [54]. These included cardiac vascular occlusion in 12% of patients (including coronary artery occlusion and myocardial infarction, sometimes preceding or concurrent with heart failure), cerebrovascular occlusion (6%), peripheral arterial occlusive events (8%), and venous thromboembolic events (5%) (Table 1) [55]. Additionally, at least 25% of patients developed hypertension. These severe safety concerns raised by the PACE trial led to the termination of the phase III EPIC trial, which was designed to compare the ponatinib versus imatinib as frontline therapy for newly diagnosed CML patients [56]. In light of the findings from the PACE trial, Ponatinib is no longer a choice of drug for newly diagnosed CML patients. Specifically, it is reserved for CML patients carrying T315I mutation or if other TKIs are not responsive. Jain et al. [57] performed a meta-analysis of several clinical trials with CML patients treated with various TKIs and found that ponatinib was associated with the highest incidence of CAEs/AOEs. To identify the recurrence of arterial occlusive events in CML patients treated with 2nd and 3rd generation TKI, Caocci et al. [49]

followed a real-life cohort of 57 adult CML patients with a previous history of AOE. Indeed, patients treated with ponatinib showed a 64 % incidence of recurrent AOE [49]. The same group of investigators demonstrated that AOE in CML patients treated with ponatinib could be predicted by the Systematic Coronary Risk Evaluation (SCORE) chart [50]. This study was performed with the real-life cohort of 85 adult CML patients who were treated with ponatinib at 17 Italian centers. Based on sex, age, smoking habits, systolic blood pressure, and total cholesterol levels, patients were stratified as per the SCORE assessment system. The increased incidence of AOE in CML patients treated with ponatinib was high to very high SCORE risk. Investigators of this study suggested personalized prevention strategies for CML patients on ponatinib based on CV risk factors [50]. Pouwer et al. [53] reported an increased risk of thrombosis and atherosclerosis in ponatinib treated animals. Pre-treatment of mice with the calcium channel antagonist, diltiazem, prior to ponatinib, reversed the pro-thrombotic phenotype suggesting that the pro-thrombotic effect of ponatinib is partially related to calcium channel activation [58]. Indeed, ponatinib-treated CML patients had increased ex vivo thrombus formation and a pro-inflammatory phenotype compared with healthy controls [53]. Taken together, the accumulating data strongly indicate that ponatinib is associated with a higher risk of cardiovascular adverse events. To further evaluate the efficacy and safety of ponatinib, a multicenter, randomized phase 2 trial (OPTIC Study) with three dosages of ponatinib (45 mg, 30 mg, and 15 mg) are currently ongoing, and results are expected later this year (2020). The outcome of this study will be critical in understanding if ponatinib mediated vascular effects are dose-dependent, and dosage reduction can lower the rate of adverse vascular effects with maintained efficacy ([ClinicalTrials.gov Identifier: NCT02467270](https://clinicaltrials.gov/ct2/show/study/NCT02467270)).

The precise mechanism of ponatinib induced adverse vascular effects are not clear. However, the broad kinase inhibition profile of ponatinib is believed to contribute to the increased incidence of adverse vascular events. Indeed, ponatinib leads to endothelial dysfunction through non-specific targeting of vascular endothelial growth factor receptors [59]. Furthermore, ponatinib leading to an increased risk of vascular occlusive events by promoting the expression of proatherogenic surface adhesion receptors [60]. Ponatinib also has direct prothrombotic effects by accelerating platelet activation and adhesion [51]. Recently, Madonna et al. [61] employed human umbilical endothelial cells (HUEVCs) to demonstrate that ponatinib-induced vascular toxicity is primarily mediated through the Notch-1 Signaling Pathway. The findings from this study revealed that ponatinib inhibits endothelial survival, reduces angiogenesis, and induces endothelial senescence and apoptosis via the Notch-1 pathway. Indeed, selective blockade of Notch-1 prevented ponatinib-induced vascular toxicity [61]. Thus, it appears that ponatinib mediated adverse vascular effects are primarily due to the off-target impacts on platelet activation and endothelial cells function. In light of all these strong clinical and experimental evidence, FDA has added a black-box warning for the safe use of ponatinib for arterial occlusion and venous thromboembolic events with the other important side effects such as heart failure. Therefore, patients on ponatinib must be informed and closely monitored for vascular AEs including, high blood pressure, thromboembolic events, evidence of arterial occlusion, and decline in cardiac function (Figure 1, Supplementary Table 1).

Preclinical studies of ponatinib cardiotoxicity

Pre-clinical screening with animal models has not been able to reliably determine which KIs will have associated cardiotoxicity. This has led to some unfortunate “surprises” once these agents have gotten into the real-world patient population. In the early clinical trials with ponatinib, very few cases of cardiotoxicity were reported [55, 62]. However, additional follow-up from various ponatinib trials has exposed a high occurrence of serious adverse cardiac events. Importantly, typical pre-clinical toxicology studies done with this agent failed to detect significant problems, highlighting the inadequacy of current approaches. We need accurate, rapidly translatable, and high throughput strategies to predict cardiotoxicity and to prevent any more of these otherwise inevitable surprises. Ponatinib is an example shown an unexpected broad spectrum of cardiotoxic complications. This toxicity is primarily due to lack of kinase selectivity, and target pathways common to both cancer and cardiac cells (Figure 2). Indeed, ponatinib is a multi-targeted kinase inhibitor that suppresses more than 60 kinases, including PDGFR, c-KIT, RET, VEGFR, and FGFR activities [45, 46, 63–84]. However, the anticancer mechanisms and the cardiotoxic mechanisms seem to be quite distinct, leading us to hope that studies to reduce the cardiotoxic effects will not diminish the anticancer effect of ponatinib. We have summarized the potential targets of ponatinib in table 2 with their implications on cardiomyocytes.

Unbiased screening experiments from multiple labs have identified ponatinib as most cardiotoxic FDA approved TKI [12, 13, 85]. To accurately predict the cardiotoxic potential of ponatinib, Talbert et al. [86] used human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CM). They showed that ponatinib rapidly inhibits prosurvival signaling pathways and induces cardiac toxicity. In an elegant study, Sharma et al. [13] have used patient-specific hiPSC-CMs and evaluated the cardiotoxicities of 21 FDA-approved TKIs. Indeed, among them, ponatinib was the most cardiotoxic TKI. Importantly, due to the well-known limitations of the cell-based models, these studies were unable to provide any extra-cardiac or organ-level effects. More recently, Hasselt et al. [85] developed an approach to predict cardiotoxicity of TKIs using clinically-weighted transcriptomic signatures. They analyzed transcriptomic profiles of TKI treated human primary cardiomyocyte cell lines with clinical data from the FDA Adverse Event Reporting System. This analysis derived clinically weighted transcriptomic signatures that may allow ranking prospective KIs for their relative risk of cardiotoxicity. We used a zebrafish transgenic BNP reporter line [12, 87] that expresses luciferase under control of the *nppb* promoter (*nppb*: F-Luciferase) to screen cardiotoxic potential of TKIs. Indeed, BNP is a well-established clinical marker of heart failure [88, 89]. Consistent with others, our *in vivo* screening predicted ponatinib as most cardiotoxic CML-TKIs. This was the first report [12] to demonstrate the ponatinib cardiotoxicity and associated molecular mechanism by employing an *in vivo* model system. This study also encourages a potential translational use of the zebrafish model for the prediction of cardiotoxicity of anti-cancer drugs.

Mechanism of ponatinib-induced cardiotoxicity

Although we are still far from a clear understanding of TKIs-induced cardiotoxicity, progress has been made to unravel the basic underlying mechanisms of TKIs mediated cardiotoxicity. In an excellent study, Sharma et al. [13] have shown that ponatinib treated

patient-specific hiPSC-CMs depicts a compensatory upregulation in cardioprotective insulin and insulin-like growth factor (IGF) signaling. This suggested that ponatinib exerts its cardiotoxicity by inhibition of growth signaling pathways. In the same line, Talbert et al. [86] also showed ponatinib induced perturbation of prosurvival signaling pathways. In our recent study [12], to mimic the real clinical scenario, ponatinib concentration was matched to serum blood concentration in treated patients. We demonstrated that ponatinib downregulates the phosphorylation of AKT and ERK. Indeed, these pathways are known to regulate cardiomyocyte survival and critical to cardiac homeostasis. Inhibition of AKT signaling has been shown to exacerbate the ischemia-reperfusion injury, pressure overload, and oxidative stress-mediated cardiac myocyte death by promoting apoptosis. Similarly, the ERK pathway is critical to myocyte survival, proliferation, and differentiation. For proof of concept, we synergistically augmented AKT and ERK signaling pathways with Neuregulin-1 β . Indeed, neuregulin-1 β treatment restored phosphorylation of AKT and ERK and cardiomyocyte viability. Taken together, ponatinib cardiotoxicity is primarily driven by an off-target effect on cardiomyocyte survival pathways. With that said, we believe that the true breadth of the cardiotoxic mechanism associated with TKIs including ponatinib requires identification of potential kinome signatures in conjunction with human adverse events databases. This will facilitate the identification of pathway-specific cardiac insult, which will allow us to mitigate the cardiotoxicity of TKIs during their preclinical development.

A cardio-oncologist view: implications for the patients care.

As the ponatinib associated cardiovascular adverse effects are getting increasingly recognized, several guidelines/recommendations/expert opinions regarding the identification, prevention, and management of cardiovascular adverse events in CML patients on ponatinib are published [48, 52, 91–94]. We refer the readers to these guidelines for detailed description; herein, we are only presenting a brief discussion with a particular emphasis on cardiotoxicity.

Before starting the ponatinib treatment, a series of baseline examinations should be performed to establish the patient's cardiovascular risk score. This should include the assessment of plasma levels of BNP and troponin, as well as detailed ECG and echocardiography [48, 93, 95]. Indeed, due to the low-cost, non-invasive nature, and repeatability, echocardiography is the preferred imaging tool for cardio-oncology patients. A detailed ECG can help to discover the signs of cardiac conduction abnormalities (QTc prolongation, atrial fibrillation, arrhythmia, etc.) [52, 93]. Initial exams should also include parameters for vascular disease risk assessment, including an ankle-brachial index (ABI), detection of atherosclerotic plaques, and intima-media thickness (IMT) by an exploration of supra-aortic and limb vessels [48, 91]). As preexisting cardiovascular comorbidities are crucial to later cardiovascular events, these baseline CVD risk assessment is vital [52, 93]. Once the basal cardiovascular risk category is established, patients should be scheduled for a long-term cardiovascular follow-up accordingly [52]. Patients with preexisting comorbidities/high-risk patients will undoubtedly benefit from the more frequent followup/monitoring. Moreover, for this high-risk patient category, it's suggested to constitute a clinical care team from the beginning. This should include the oncologists, cardiologists, and hematologists [48, 91, 94].

Patients on ponatinib therapy must be regularly monitored for cardiac function and conduction abnormalities, hypertension, vascular AEs. It is believed that ponatinib mediated CVD adverse effects are dose-dependent; therefore, a prompt dose adjustment and close follow up is critical to ensure a balance between efficacy and safety [93]. As discussed above, the approved dose for ponatinib is 45 mg once a day. It is recommended that this dose should only be prescribed until a complete cytogenetic response (CCyR) or major molecular response (MMR) is achieved. After that, a dose reduction should be considered as per patients' CVD monitoring data [48, 52, 91].

Furthermore, for patients with high CVD risk category, it's advised to adjust the starting dose to 30–15 mg/day, and consider to increase if the anti-oncogenic response is not satisfactory. In the latter case, CVD risk should be closely monitored and carefully managed [48, 91]. Indeed, the FDA recommends stopping the ponatinib treatment if there are serious ischemic events like MI or stroke [92]. Additionally, it is suggested not to restart the treatment unless there are no other treatment options available, and the potential benefit surpasses the risk of subsequent ischemia. Of note, the cardiotoxicity is often reversible with drug interruption. For the low-risk category, treatment should be continued on the selected dose with regular monitoring of CVD risk every three months [92, 95]. More frequent monitoring (every 2-3 weeks) should be considered if the patient is developing any sign of cardiotoxicity, e.g., a decline in ejection fraction. If the patient develops symptoms of overt heart failure, it should be treated with standardized therapy as per clinical indication [48, 91]. If the symptoms of congestive heart failure further worsen, the discontinuation of treatment should be considered. Thus, a baseline risk assessment, careful follow-up, dose adjustment, and a multidisciplinary collaborative effort to patient care are essential to ensure an optimal balance of risk and benefit of ponatinib treatment.

Conclusion and future perspectives

The emergence of cardiotoxicity is one of the primary limitations of anticancer therapeutics and has a strong effect on patient quality of life and survival. To diminish the risk of cardiac diseases, cardiologists should be aware of the potential cardiotoxic effects of anticancer drugs. Ponatinib is the only TKI that works effectively against T315I mutation +tive CML patients. Ponatinib granted accelerated approval because of its clinical efficacy. In phase I trial of ponatinib, responses were observed at the lowest dose levels. It was found that daily doses of 15–45 mg would achieve serum drug concentrations predicted to suppress the T315I mutations in preclinical studies. Consequently, the approved daily dose of 45 mg may not have been ideal in terms of efficacy and safety, because further studies and trials showed a clear association between dose intensity and appearance of cardiovascular adverse events. Although clinical trials provide a good baseline reference point for the approval of a cancer drug. But, the real patient population is multifactorial, and the cumulative effect of various co-morbidities or other complications may give rise to synergistic cardiotoxic effects that are underreported in preclinical studies. While there is a growing body of evidence and an increased understanding of the pathogenesis of ponatinib-induced cardiotoxicity, the process of determining how best to manage and prevent major cardiotoxicities remains a significant challenge. Oncologists, in collaboration with multidisciplinary teams, have the delicate responsibility of identifying the proper treatment combination that will maximize tumor

response while minimizing adverse outcomes. More intense scrutiny of cardiac complications in preclinical studies are warranted for upcoming TKIs before FDA approval. Additionally, determination of cardiotoxic mechanisms necessitates the identification of the specific target, inhibition of which is responsible for cardiotoxicity. This identification of the critical target accomplishes two things. First, once a tyrosine kinase is recognized as playing a vital function in the heart, all subsequent kinase inhibitors that target that kinase will be suspect. Thus, one should be able to predict cardiotoxic agents, prior to their release. Second, the identification of targets facilitating cardiotoxicity can help guide future drug design by avoiding “bystander” targets. Therefore, approaches could be developed that would block drug-induced activation of the pathway in the heart that is responsible for cardiotoxicity but would leave tumor cell killing intact. The conjunction of FDA Adverse Event Reporting System and clinically-weighted transcriptomic signatures will provide significantly deeper insight to target genes in relation to cardiotoxic mechanisms of TKIs. This will enable better precautions and monitoring of adverse effects associated with these agents during drug development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- New, growing, but well-established discipline “cardio-oncology” focuses on the monitoring, prevention, and treatment of cardiovascular complications associated with cancer therapeutics.
- Radiation and chemotherapy-induced cardiotoxicity are well established. However, the cardiotoxicity associated with targeted therapies (kinase inhibitors (KIs)) is less recognized.
- Multiple labs have identified ponatinib as most cardiotoxic KI among the entire FDA approved KI family.
- Of note, Ponatinib is the only treatment option for CML patients with T315I mutation.
- This review focusses on the cardiovascular risks and mechanism/s associated with CML KIs with a particular emphasis on ponatinib cardiotoxicity.

Figure 1:
Roadmap of ponatinib development and clinical trials.

Figure 2:

Signaling pathway inhibition by ponatinib in chronic myeloid leukemia and cardiomyocytes.

(A) Ponatinib inhibits all BCR–ABL-dependent phosphorylation and signaling events, leading to the reversal of pro-survival effects and activation of apoptosis in leukemic cells.

(B) In cardiomyocytes, ponatinib rapidly inhibits prosurvival signaling pathways leading to cardiomyocytes apoptosis and cardiac dysfunction. BAX, BCL2 associated X protein; BAD, BCL2-antagonist of cell death; ERK, extracellular signal-regulated kinase; FOXO3A, forkhead box O3A; GAB2, GRB2-associated binding protein 1; GRB2, growth factor

receptor-bound protein 2; MEK, mitogen-activated ERK kinase; PIP3, phosphatidylinositol trisphosphate; PI3K, phosphatidylinositol 3-kinase; SOS, son of sevenless; STAT5, signal transducer and activator of transcription 5.

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Table 1:

Tyrosine kinase inhibitors and related cardiac adverse events

Tyrosine kinase inhibitor	Cardiac adverse events	Reference
Imatinib	Edema, pericardial effusion, peripheral edema, pulmonary edema, angina pectoris, hypotension, palpitation, flushing, arrhythmia, atrial fibrillation, tachycardia, cardiac tamponade, acute coronary syndromes, HF, left ventricular dysfunction, cardiogenic shock, hypertension, MI, pericarditis, thrombosis	[16, 29–32]
Nilotinib	Peripheral edema, hypertension, arterial stenosis, QTc prolongation, sudden death, ischemic heart disease, peripheral arterial occlusive disease, ischemic cerebrovascular events, angina pectoris, arrhythmia (AV block, atrial fibrillation, bradycardia, cardiac flutter, extrasystoles, tachycardia), palpitations, flushing, pericardial effusion, aortic valve sclerosis, arteriosclerosis, HF, cardiomegaly, MI, pulmonary edema	[33–38]
Dasatinib	QTc prolongation, angina pectoris, pericardial effusion, left ventricular dysfunction, HF, cardiomyopathy, diastolic dysfunctions, fatal MI, pericardial effusion, palpitations, pulmonary arterial hypertension	[32, 38, 39]
Bosutinib	Edema, pericardial effusion, angina pectoris, pericarditis, QTc prolongation	[32, 38, 40, 41]
Ponatinib	Vascular occlusion events, hypertension, peripheral edema, left ventricular dysfunction, HF (including fatalities), pulmonary edema, cardiogenic shock, ischemia, MI, stroke, arrhythmia, QTc prolongation	[38, 42, 43]

Table 2:

Ponatinib targets and their implication on cardiomyocytes

S.No.	Ponatinib Target	Disease	Studied cell lines	Implication on cardiomyocytes	Reference
1.	FGFR1	Myeloproliferative syndrome	Transformed murine BaF3 cells, human KG1 cells, small cell lymphocytic lymphoma cells	Altered cardiomyocyte proliferation and differentiation	[76, 82]
		Lung cancer	Non-small cell lung cancer (NSCLC) cell lines		[46, 77]
		Neuroblastoma	NB cell lines (CHP-134, CHP-212, NGP, LAN-5, SH-EP, SK-N-AS, SK-N-BE and SK-N-SH)		[66, 90]
		Small cell carcinoma of the ovary	BIN67 and SCCOHT-1 cells		[64]
		Malignant rhabdoid tumors	MRT cell lines (A204 and G402)		[70]
2.	FGFR2	Endometrial cancer cells	EC cell lines MFE-296, AN3CA, MFE-280	Altered cardiomyocyte proliferation and differentiation, less cardiac hypertrophy and fibrosis upon inhibition	[71, 80]
		Gastrointestinal stromal tumor	GIST-derived cell lines		[74]
		Breast cancer	MDA-MB-231		[46]
		Neuroblastoma (NB)	NB cell lines (CHP-134, CHP-212, NGP, LAN-5, SH-EP, SK-N-AS, SK-N-BE and SK-N-SH)		[66, 90]
3.	FGFR3	Bladder cancer	Bladder cancer cells	Altered cardiomyocyte proliferation and differentiation	[46]
		Neuroblastoma (NB)	NB cell lines (CHP-134, CHP-212, NGP, LAN-5, SH-EP, SK-N-AS, SK-N-BE and SK-N-SH)		[66, 90]
4.	FGFR4	Hepatocellular carcinoma	HCC cell lines MHCC97L, MHCC97H, HepG2 and SMMC7721	Less cardiac hypertrophy and fibrosis upon inhibition	[68]
		Neuroblastoma (NB)	NB cell lines (CHP-134, CHP-212, NGP, LAN-5, SH-EP, SK-N-AS, SK-N-BE and SK-N-SH)		[66, 90]
		Rhabdomyosarcoma	RMS cell lines (RH28, JR, RH18, RD, CTR, BIRCH, TTC-516, TTC-442, RH30, RH4, RH5, RH41, and RH36)		[79]
5.	FLT3	Acute myeloid leukemia	MV4-11, Ba/F3-ITD-676, Ba/F3-ITD-691, and Ba/F3-ITD-697	Cardiomyocyte death	[83, 84]
		Neuroblastoma	NB cell lines (CHP-134, CHP-212, NGP, LAN-5, SH-EP, SK-N-AS, SK-N-BE and SK-N-SH)		[66, 90]
6.	PDGFR α	Small cell carcinoma of the ovary	BIN67 and SCCOHT-1 cells	Less cardiac fibrosis upon inhibition	[64]
		Malignant rhabdoid tumors	MRT cell lines (A204 and G402)		[70]
		Neurofibromatosis type 2	Merlin-deficient HSC line		[65]
		Chronic eosinophilic leukemia	EOL-1, BaF3 cells		[72, 73]
7.	RET	Thyroid cancer	TT thyroid cancer cell lines	Not expressed in cardiomyocytes	[81]
		Lung cancer	Non-small cell lung cancer (NSCLC) cell lines		[75]

S.No.	Ponatinib Target	Disease	Studied cell lines	Implication on cardiomyocytes	Reference
		Medullary thyroid cancer	Human TT, MZ-CRC-1 and TPC-1 thyroid carcinoma cells		[78]
8.	c-KIT	Neuroblastoma	NB cell lines (CHP-134, CHP-212, NGP, LAN-5, SH-EP, SK-N-AS, SK-N-BE and SK-N-SH)	Not expressed in adult cardiomyocytes	[66, 90]
		Liposarcoma	human liposarcoma cell lines (SW872, LP6, SA-4, LiSa-2, FU-DDLS-1, LPS141, GOT-3, MLS-402, T778 and T1000)		[67]
		Gastrointestinal stromal tumor	GIST-derived cell lines		[74]
9.	PDGFR	Neuroblastoma	NB cell lines (CHP-134, CHP-212, NGP, LAN-5, SH-EP, SK-N-AS, SK-N-BE and SK-N-SH)	Altered contractility	[66, 90]
10.	PDGFR β	Infantile myofibromatosis	Mutant transfected MCF7 and HEK-293T cell lines	Altered contractility	[69]
		Neurofibromatosis type 2	Merlin-deficient HSC line		[65]
11.	c-SRC	Chronic myeloid leukemia	BaF3 cell lines	Altered contractility	[45]
		Neurofibromatosis type 2	Merlin-deficient HSC line		[65]
12.	VEGFR1	Neuroblastoma	NB cell lines (CHP-134, CHP-212, NGP, LAN-5, SH-EP, SK-N-AS, SK-N-BE and SK-N-SH)	Altered contractility	[66, 90]
13.	VEGFR2	Chronic myeloid leukemia	BaF3 cell lines	Altered contractility	[45]
		Medullary thyroid cancer	Human TT, MZ-CRC-1 and TPC-1 thyroid carcinoma cells		[81]
14.	c-Jun	Breast cancer lung metastasis	MDA-MB-231	Cardiomyocyte apoptosis	[63]