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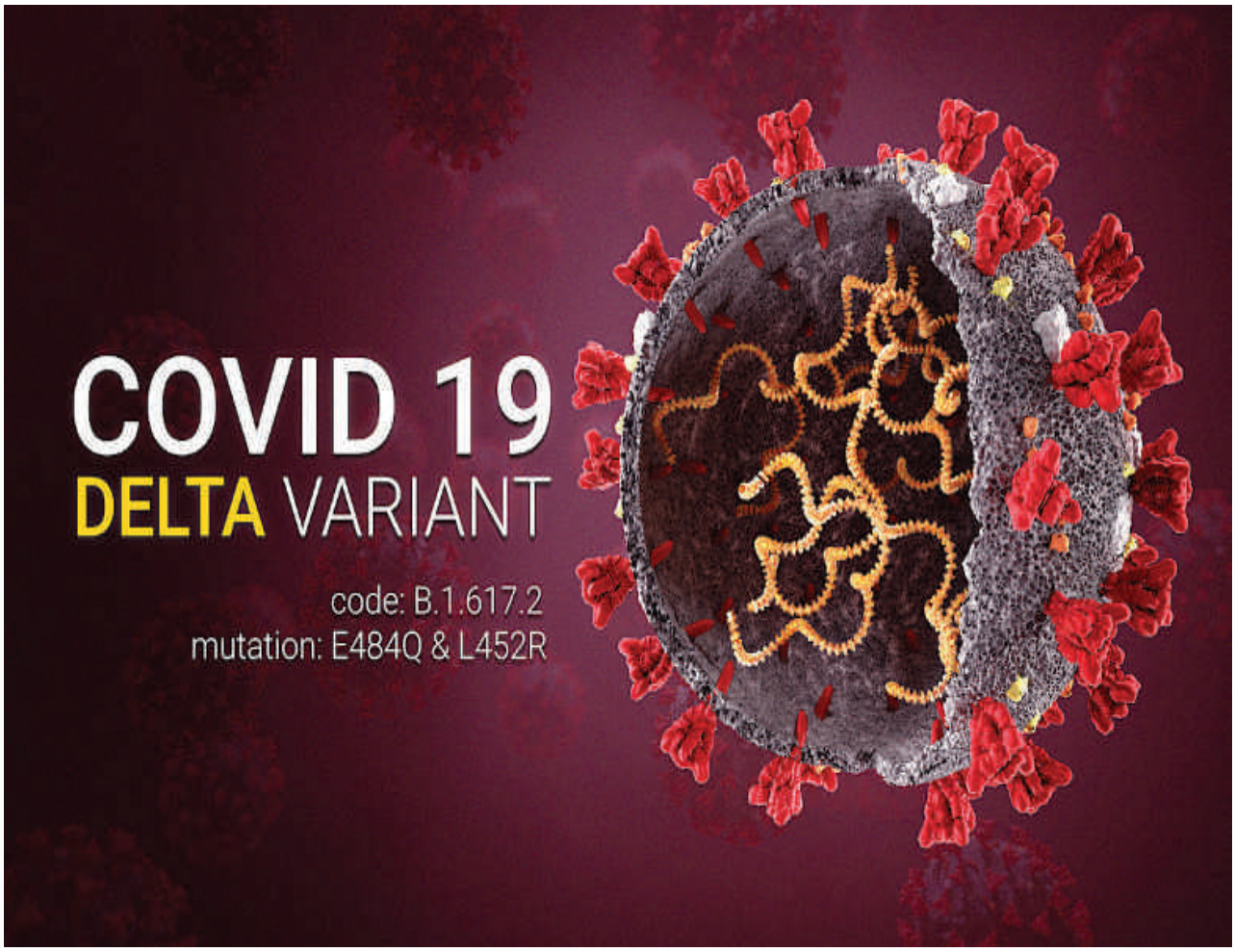

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Review Article

Cardiovascular Toxicity Associated With Tyrosine Kinase Inhibitor Therapy In Chronic Myeloid Leukemia

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Abstract

Treatment of Chronic myeloid leukemia (CML) typically entails a long–term course of tyrosine kinase inhibitors (TKI) therapy. This review provides a summary on the cardiotoxic effects of TKIs. Five small molecular TKIs were evaluated in our review. The cardiotoxic effects of TKIs can range from superficial edema to potentially fatal conditions such as congestive heart failure (HF) and acute coronary syndrome (ACS). With the constant introduction of newer generations of TKIs, it has been demonstrated that different TKIs have distinct cardiovascular safety profiles. Amongst which, the first–generation TKI – imatinib appears to have the safest profile, mainly causing edema along with nausea, rash and muscle cramps. Other TKIs, like the second–generation dasatinib, bosutinib, and nilotinib, have shown an increased incidence of pleural effusion and QT prolongation. Ponatinib, a third generation TKI, has shown a relatively high incidence of serious adverse effects including thrombotic vascular occlusion and heart failure, particularly in patients with a prior history of cardiovascular impairment. Therefore, it is advisable that at–risk patients taking TKIs be screened with an Electrocardiogram (ECG) and have a careful cardiovascular risk assessment before starting TKI therapy to avoid potential cardiotoxic effects such as arrhythmias, acute coronary syndrome (ACS), congestive heart failure, and pleural effusion.

Keywords: tyrosine kinase inhibitor, TKI, chronic myelogenous leukemia, CML, cardiotoxicity, side effects, imatinib, dasatinib, bosutinib, nilotinib, ponatinib

Introduction

Among anti–neoplastic medications, few have had such a radical impact on the natural history of a disease as Tyrosine Kinase Inhibitors (TKIs). The identification of the BCR–ABL fusion protein in the 1980s paved the way for the development of targeted cancer therapy for Chronic Myeloid Leukemia (CML).[1] This paradigm shift in the therapeutic approach demonstrably translated into significant improvements in the 10–year survival rates, and thus became the standard of care for CML patients.[2]

Tyrosine Kinase Inhibitors (TKIs), exert their effects by inhibiting the enzymatic activity of kinases involved in phosphorylation of tyrosine molecules on several intracellular and cell surfaces signaling proteins. This phosphorylation is implicated in activating a cascade of many cellular functions, such as other enzymatic activity, gene activation, protein synthesis, cellular survival, and apoptosis. Multiple tyrosine kinase receptors have been identified and each has been implicated in mediating specific effects. TKIs act as selective inhibitors of their tyrosine kinase targets.[3] As a result of this, the adverse effects of TKIs are thought to be mediated by both the on–target – namely, c–Abl – as well as off–target sites.[3]

In the landmark IRIS trial, although a safer profile – in comparison to the conventional therapy – was described – many adverse effects of both hematological and non–hematological nature were reported with imatinib. Hematological adverse effects being mainly, neutropenia, anemia and thrombocytopenia. Non–hematological

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adverse effects were mainly of gastrointestinal, and cardiovascular nature – these included nausea, fatigue, and edema. Of these, superficial edema was the most frequently reported manifestation. Edema was purported to be due to fluid retention and is mainly periorbital in its distribution. Pleural effusion, ascites, and lower limb edema have also been reported.

Since patients with CML are prescribed a long course of therapy, long–term adverse effects should be considered. Some of the more serious cardiotoxic effects such as LVEF reduction, QT prolongation, peripheral arterial disease, acute coronary syndrome (ACS), pleural effusion and pulmonary arterial hypertension have also been described in the literature – with distinctive patterns of cardiotoxic manifestations among individual TKIs.[4] Among the small molecular TKIs — imatinib appears to have the safest profile, primarily causing superficial edema.[5] Others, such as dasatinib and nilotinib have been associated with pleural effusion and QT prolongation, while a more recent drug — ponatinib has been associated with fatal heart failure, arrhythmias and increased incidence of thrombotic vascular occlusive events.[5–8]

Most adverse effects of TKIs usually arise within three months of drug initiation, still, cardiotoxic effects can take up to a few years to develop. The long–term effects of TKIs, however, remain unclear as many of the trials are constrained by a relatively short follow–up period. Most of these AEs can be successfully managed by symptomatic treatment, dose modification or drug discontinuation. Drug resistance in advanced disease is the primary cause of switching to another TKI, yet patients who require a different drug due to resistance appear to have a higher incidence of cardiovascular adverse effects. [9] Table 1 compares cardiovascular side effects of the 5 TKIs discussed in this paper **(Table 1.)**

Imatinib

Imatinib mesylate is one of the foremost tyrosine kinase inhibitors developed as a targeted inhibitor of BCR–ABL1 tyrosine kinases. In its earliest clinical study for Chronic Myeloid Leukemia (CML) – the IRIS trial – imatinib showed superior results over the prior standard treatment – interferon alfa and cytarabine.[10] Imatinib demonstrated higher rates of cytogenetic and molecular responses when compared with interferon alfa and cytarabine and it had fewer observed adverse effects than the latter. This led to imatinib becoming the first–line treatment of CML.[2] Currently, imatinib is also utilized in the treatment of Philadelphia chromosome–positive Acute Lymphoid leukemia (ALL) and Gastrointestinal Stromal Tumors (GIST).

Imatinib is a small molecular TKI that exerts its antineoplastic effect by inhibiting the catalytic activity of the BCR–ABL1 fusion protein, PDGF receptor, and KIT tyrosine kinase protein. In the IRIS trial (n=551), 7.1% of patients (n=39) had experienced serious cardiotoxic effects while on imatinib. It also reported edema (including peripheral and periorbital edema of all grades) in more than half (55.5%) of patients.[8] Additionally, nausea (44%), muscle cramps (38%), muscle pain (37%), rash (34%), fatigue (34%), diarrhea (33%) and headaches (31%) were many of the frequently reported adverse effects. Several other studies reported a number of patients presenting with varying degrees of edema. [5,10,11] Thus, fluid retention remains one of the most common adverse effects of imatinib. [5]

Before imatinib, HER2/neu inhibitors such as trastuzumab were used as part of the treatment for certain breast malignancies – trastuzumab was associated with a number of congestive heart failure cases among recipients. [12] Similarly, small molecular TKIs were suspected of having similar cardiotoxic effects. In the following years of the IRIS trial, multiple non–clinical studies had been published with conflicting results about the effects of imatinib on cardiac function. The first of these was a retrospective study (n=10) that reported an increased incidence of CHF among patients on imatinib therapy. The same study evaluated the cellular changes found in the *in vitro* cardiomyocytes which exhibited a stress response after the administration of imatinib. Moreover, exposure

TKIs	Myocardial Dysfunction	Edema/ Fluid Retention	Pulmonary Arterial Hypertension	Thrombotic Events	QT Prolongation
Imatinib	+	++	–	–	–
Dasatinib	+	++*	++	–	+
Nilotinib	+	+	–	+	++
Bosutinib	–	++	–	–	+
Ponatinib	++	+	–	+++	–

Table 1: Cardiovascular side effects of the 5 TKIs
*Most notable is pleural effusion

to imatinib produced endoplasmic reticular stress along with mitochondrial membrane damage, thus priming myocytes for cell death. This decrease in cardiomyocytes was thought to be the proposed mechanism of supposed reductions in left ventricular ejection fraction (LVEF) eventually leading to the actuation of congestive heart failure in these patients.[13] However, subsequent studies conducted in clinical settings, with a larger sample size, failed to replicate similar findings of CHF incidence in patients. In one study (n = 1276), the prevalence of CHF in patients receiving imatinib was reported to be 1.7%. Other studies have continued to show that the incidence of CHF in imatinib–treated patients has remained low.[14]

However, it is certainly possible that pre–existing CHF may be exacerbated by fluid retention after the administration of imatinib. However, the current evidence does not support imatinib as a causal factor in the development of CHF. Despite this, it remains unclear whether imatinib can precipitate CHF among patients with prior renal and cardiovascular impairment.[15,16] Prospective studies in this matter are lacking – one study that assessed patients treated with imatinib over a period of 1 year reported no deterioration in the left ventricular function.[17] However, a similar study conducted with a shorter period included patients (n = 55) with Gastrointestinal Stromal Tumor (GIST) and reported increases in patient brain natriuretic peptide (NT–proBNP) levels among 4% of the patients (n= 2).[18] Further studies are required – that which evaluate imatinib's long–term cardiotoxic effects and particularly, prospective evaluations of imatinib's adverse effects in order to circumvent biases intrinsic to retrospective studies.

As mentioned earlier, Peripheral Arterial Diseases (PAD) have also been observed in association with tyrosine kinase inhibitors. In the Evaluating Nilotinib Efficacy and Safety in Clinical Trials–Newly Diagnosed Patients (ENESTnd trial), imatinib was, however, associated with a lower risk of Peripheral Arterial Occlusive Disease (PAOD) when compared to nilotinib – alluding to a possible protective mechanism of imatinib.[8,19] Studies also show that imatinib – unlike other TKIs – has been associated with lower fasting blood–sugar and control of refractory pulmonary arterial hypertension (PAH).[20,21]

Dasatinib

Dasatinib is a second–generation small–molecular TKI developed initially as a second–line treatment for imatinib–resistant CML patients. Like imatinib – it inhibits the BCR–ABL and KIT tyrosine kinase receptors, PDGF receptor with additional effects on SRC receptor. The Dasatinib vs Imatinib Study in Treatment Naïve CML Patients (DASISION) was one of the initial clinical trials to report the safety and efficacy of dasatinib in comparison with imatinib. Dasatinib – in comparison with imatinib – showed increased complete cytogenetic response <12 months – which confers a favorable long–term prognosis.[6] It is also less susceptible to disease resistance. When compared with imatinib, dasatinib has been described as more potent in its effect on BCR–ABL receptors – with *in vitro* studies suggesting up to 325 times more potency than that of imatinib.[22]

QT prolongation has been associated with dasatinib use – therefore, obtaining ECG and serum electrolytes prior to its initiation is recommended, especially in patients at higher risk, such as those with pre–existing heart conditions or the presence of drug interactions. In its initial report, the DASISION trial did not report an increase in cardiotoxic effects among the dasatinib arm. However, as the trial accumulated long term data – it has become evident that dasatinib has a different cardiotoxic profile when compared to imatinib. Of particular importance, is the increased propensity of dasatinib – among other TKIs – to cause pleural effusion. Other significant adverse effects include pericardial effusion, PAD, and Pulmonary Arterial Hypertension (PAH). Edema has also been reported with dasatinib albeit, rarer than imatinib.[6,7]

Dasatinib had an FDA–warning issued on its cardiovascular effects mainly based on ischemic events (3.9%), arrhythmias (7%) and fluid retention (8.5% including pleural effusion).[19,23] As the current literature suggests that pleural effusion, arrhythmias, PAH and PAD occur at a higher rate with dasatinib, the patient should be closely observed for cardiac and pulmonary deteriorations and referred to cardiology if sufficient suspicion has been established.

Nilotinib

Nilotinib is a small molecule tyrosine kinase inhibitor designed and approved for imatinib–resistant Chronic Myelogenous Leukemia (CML) and for the treatment of patients with newly diagnosed Chronic Myeloid Leukemia (CML) in chronic phase. Similar to other TKIs, common side effects include fatigue, headache, nausea, diarrhea, muscle, and joint pain. Nilotinib also has an effect on the cardiovascular system.

The incidence of nilotinib–induced Cardiovascular Events (CVEs) has been reported over a wide range – 1.3%–35%.[24,25] In contrast to previous studies reporting a high incidence of CVEs, a 2017 study noted a low incidence of CVEs in CML patients with long–term exposure to nilotinib.[26]

However, the possibility of vascular events should be considered when selecting nilotinib for the treatment of

CML patients with known risk factors for vascular disease. The incidence of PAOD events in patients with CML–CP receiving nilotinib was found to be higher than in those receiving imatinib by a retrospective cohort analysis.[24]

Although nilotinib is rarely associated with clinically relevant vascular events, it has been associated with side effects such as elevated lipase and/or amylase levels, pancreatitis, and hyperglycemia.[27] QT prolongation, changes in LVEF, and clinical cardiac adverse events were found to be uncommon in patients treated with nilotinib and seldom led to treatment discontinuation. Although 20% of patients developed new electrocardiographic abnormalities, some of whom developed severe coronary artery disease.[28]

It has been noted that co–administering nilotinib with doxorubicin results in a dramatic increase in systemic doxorubicin with a concomitantly increased risk of cardiotoxicity.[29] Finally, a recent case report from China reported the development of acute ischemic intestinal necrosis in a CML patient on nilotinib, as a rare side effect.[30]

Bosutinib

Bosutinib is a synthetic quinolone derivative. When compared to other TKIs, bosutinib is considered to have a more favorable hematologic toxicity profile.

A long–term evaluation of bosutinib–treated CML patients highlighted that relative to other new–generation TKIs, vascular, and cardiac Treatment Emergent Adverse Events (TEAEs) incidences were generally low, with dose adjustments and discontinuations due to these events being rare.[31] Notably, pericardial effusion was the only individual cardiac TEAE to occur at a significantly higher incidence with bosutinib versus imatinib, though infrequent.[31] Indeed, bosutinib›s lower toxicity profile could be attributed to its lack of c–KIT and PDFR activity.

The incidence of pleural effusions during bosutinib use has been reported as 1–10%. [32] Bosutinib has also been linked with worsening of pre–existing Pulmonary Arterial Hypertension (PAH), in a patient who experienced improvement upon withdrawal but later further deterioration after commencing ponatinib.[33]

Ponatinib

Ponatinib is a novel, orally active TKI structurally designed to target the BCR–ABL T315I mutation after the mutation was shown to confer resistance to both imatinib, and second–generation TKIs such as dasatinib and nilotinib. After the PACE trial[34], ponatinib obtain a fast–track FDA–approval for the treatment of resistant or intolerant to prior TKI CML in December 2012.

The most common side effects observed in a phase II trial of ponatinib included vascular occlusion (23%), thrombocytopenia (37%), and neutropenia (19%), with 18/449 patients dying during the study.[34] In 2013, a randomized phase III trial of ponatinib versus imatinib in newly diagnosed CP–CML "EPIC trial" was terminated after the observation of arterial thrombotic events in 27% of patients during the study period. None of the prospectively defined endpoints could be analyzed due to that and the study termination was followed by FDA drug safety warning and ponatinib marketing suspension.[35]

A study involving a targeted *in vivo* and *in vitro* cardiotoxicity screen of all approved CML TKIs identified ponatinib as the most cardiotoxic drug, which was found to induce cardiomyocyte apoptosis.[36] The dose of ponatinib was found to be significantly associated with increased risk of adverse events. A predicted reduction of approximately 33% in the risk of an arterial thrombotic event was calculated for each 15 mg dose reduction. However, a multivariate analysis has shown that it might take up to 6–month delay between dose alteration and risk manifests for some arterial occlusive events resulting change in event risk.[37] Other risk factors that have been identified including obesity, older age, hypertension, history of diabetes, history of smoking, hypercholesterolemia, and higher baseline platelet level. However, vascular occlusive events also occurred in young patients without risk factors. [37]

Preetesh Jain et al reviewed the cardiovascular or arteriothrombotic adverse events (CV– or AT–AEs) in CML patients on TKIs. Ponatinib was reported to have the highest CV–AE and AT–AE incidence ratios (IRs) with 40.7 (95% CI; 27.9–59.4) and 9.0 (95% CI; 4.1–20.1) risk for each, respectively.[38] An increase in the rates of fatal myocardial infarction has been observed in patients treated with ponatinib,[34,38] with cardiovascular complications including cardiomyopathy, congestive heart failure, and vascular occlusion.[34,36–37] A low risk of QTc prolongation has been observed in patients treated with ponatinib.[39] Ponatinib–associated Pulmonary Arterial Hypertension (PAH) has also been reported.[40]

Conclusion

With advancements in cancer treatment at the forefront of medical advancements, it is imperative that development of tyrosine kinase inhibitors continue along similar lines. There is a need to clearly identify and quantify major toxicities associated with TKIs, and search for safer alternatives. With improved pre–clinical screening of anticancer agents and clear guidelines on pre–treatment cardiac evaluation and monitoring of patients, adverse cardiovascular toxicities of those agents can be minimized.

In conclusion, through this review, we shed light on the cardiotoxicity profiles of 5 TKIs used for CML, namely imatinib, dasatinib, nilotinib, bosutinib and ponatinib. With further elucidation of safety profiles and adverse effect mechanisms, clinicians can be better guided to make the most appropriate treatment decisions for their patients.

Conflict of Interest: The authors declare that they have no conflicts of interest.

Human and animal rights: The article does not contain any studies with human and animal and this study was performed following institutional and national guidelines.

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