



## Tyrosine kinase inhibitors induced cardiotoxicity

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### ABSTRACT

Tyrosine kinase inhibitors (TKI) have emerged as an important new class agents of the treatment of diverse tumors. Cardiotoxicity is one of the most common adverse effect of TKI. A careful initial evaluation before starting potentially cardiotoxic cancer treatment and optimal control of pre-existing cardiovascular risk factors, followed by ongoing cardiac safety monitoring, treatment of early signs of cardiovascular toxicity and timely implementation of preventive or therapeutic measures is essential task in treatment of cancer patients. It is important to identify TKI induced cardiotoxicity and start treatment as early as possible because timely undiagnosed disease can lead to unsuccessful treatment of cancer, increased mortality and the deterioration of the quality of life. This review provides an overview of the latest scientific data on the TKI induced cardiovascular diseases mechanisms, epidemiology, clinical signs, diagnosis and treatment recommendations.

**Key words:** cancer, tyrosine kinase inhibitors, cardiotoxicity, complications

**List of abbreviations:**

**TK** – tyrosine kinases

**TKI** – tyrosine kinase inhibitors

**RTK** - receptor tyrosine kinase

**CML** - chronic myeloid leukemia

**GIST** - gastrointestinal stromal tumors

**PERK** - protein kinase RNA-like endoplasmic reticulum kinase

**PKC- $\delta$**  - protein kinase C delta type

**PDGFR** - platelet - derived growth factor receptor

**VEGFR** - vascular endothelial growth factor receptor

**CHF** - congestive heart failure

**LVEF** - left ventricular ejection fraction

**Introduction**

Nowadays targeted therapy became a powerful tool in cancer treatment, with significant benefits in terms of survival (1). Chemotherapy is frequently used in cancer therapeutics in modern medicine, along with targeted therapy, radiation therapy and surgery (2). Traditional chemotherapy such as alkylating agents and antimetabolites is associated with a wide range of side effects, for example gastrointestinal symptoms, alopecia and even lethal adverse effects, such as bone marrow suppression. These reaction's negatively affect's quality of life of cancer patients.

In targeted cancer therapy, drugs affects key signaling molecules and inhibits oncogenesis and metastasis with other profile of adverse effects (3). There are 518 kinases in human kinome, 90 of them - tyrosine kinases (TK's) (4) which is a central role in controlling homeostasis (cell growth, differentiation, migration and apoptosis) (5,6). Mutations of TK's cause defective signaling into cells and results in tumor growth and metastasis. Targeted key TK's is a proven remarkable

achievement in treating malignancy. The two main agent's categories of targeted cancer therapy are TK antibodies (trastuzumab, rituximab, alemtuzumab etc.) and TK inhibitors (TKI's) (sunitinib, sorafenib, dasatinib, nilotinib, imatinib etc).

However, targeted cancer therapy-induced cardiovascular toxicities are sometimes critical issues in patients who receive novel anticancer agents, such as trastuzumab, bevacizumab, sunitinib, sorafenib, axitinib, dasatinib, nilotinib, imatinib and others. Cardiotoxicity is a very important adverse effect and may be associated with traditional and targeted therapy agents and is divided into two categories, type I and type II, based on distinct pathological changes and clinical characteristics (7). Anthracyclines can be an example of type I agents. Type I agents cause irreversible damage to cardiomyocytes, such as vacuole formation, contractile element fall, or even necrosis (8). TKI's are the type II category agents that result in lesion of cardiomyocytes, with reversible cardiac function changes. In addition to cardiac dysfunction, targeted cancer therapy-induced

cardiotoxicities could manifest as elevated blood pressure, thromboembolism, pericardial thickening and arrhythmia (9).

### **Small molecule TKI's**

ATP analogues block the catalytic site of receptor tyrosine kinase (RTK) in cancer cells applies to design small-molecule TKI's, all of which exhibit very high affinity for the ATP pockets of the TK's, so that the substrate protein cannot get access to the kinase site or be phosphorylated. The risk of TKI-associated cardiotoxicity is relatively low (10). Small molecules are tentatively considered as type II agents, due to the reversibility of the adverse effects and lack of cumulative dose - dependent effects. On-target cardiotoxicity occurs when the therapeutic drug functions on the intended target kinases and allied kinases in cardiomyocytes (11). The representative drug of off-target cardiotoxicity is sunitinib (12).

### **Imatinib mesylate**

Imatinib has been approved by the FDA as an oral drug for the treatment of chronic myeloid leukemia (CML), gastrointestinal stromal tumors (GIST's) and hypereosinophilic syndrome. Imatinib is a revolutionary drug for the treatment of CML by targeting ABL (13). It efficiently inhibits BCR- ABL+ CML cells, blocks phosphorylation and cause apoptotic cell death. Although imatinib cannot cure CML, it converts CML into a manageable chronic disease. The best known imatinib targets are ABL and platelet-derived growth factor receptors ( $\alpha$  and  $\beta$  PDGFR's).

Overall, imatinib is well tolerated. Although the incidence of edema and dyspnea are reported to be as high as 16%. Investigation using imatinib-treated cardiac cells revealed that by inhibiting ABL, imatinib induced endoplasmic reticulum stress by activating protein kinase

RNA-like endoplasmic reticulum kinase (PERK), protein kinase C delta type (PKC- $\delta$ ) and inositol-requiring enzyme 1 pathways. All these events caused the release of BCL- 2- associated protein and were followed by mitochondrial depolarization, ATP depletion, cytochrome c release and eventually resulted in necrotic and apoptotic cell death (14). In addition, imatinib may affect cardiac progenitor cells in human heart by blunting c-Kit which is preserved in this cell group (15).

### **Sunitinib**

Sunitinib is a multiple TK inhibitor with more than 50 known targets, including VEGFR 1- 3, PDGFR- $\alpha$  and  $\beta$  and RET proto-oncogene (16). Sunitinib is the first TKI approved by the FDA to be used in two different cancers - GIST and metastatic renal cell carcinoma (mRCC), with significant survival benefits (17). In tumor cells, sunitinib simultaneously inhibits the VEGFR PI3K mammalian target of rapamycin signaling pathway, RET, FMS-like tyrosine kinase-3 and their mutual downstream target, signal transducer and activator of transcription, to induce tumor cell apoptosis and growth arrest. Angiogenesis was also found to be inhibited by blocking the autocrine and paracrine effects of PDGFR in breast cancer cell lines (18,19).

Sunitinib adverse events are considered as manageable. The most frequent cardiac adverse events in sunitinib patients are arterial hypertension and congestive heart failure (CHF). The incidence of sunitinib-associated CHF ranges from 2,7 to 15% (20,21%). Recent surveys show that longer exposure to sunitinib may be required for patients to develop CHF. Abnormal mitochondrial biogenesis was observed on transmitted electron microscopic examination, including membrane whorls in sunitinib-treated mice. In sunitinib-cultured neonatal rat ventricular myocytes, cytochrome C was released, caspase-9 was activated and apoptotic death was detected

by the TUNEL assay (20). Kerkela et al (12) reported an off-target mechanism of inhibition of AMP- activated protein kinase (AMPK). AMPK is a cellular energy generation switch. When cellular energy levels decrease, AMPK is activated to stimulate ATP production through catabolic pathways, while inhibiting energy-consuming pathways. Sunitinib induces myocyte loss in animal models. Loss of myocytes may be prevented by gene transfer of a constitutively active mutant AMPK, suggesting it was directly inhibited by sunitinib and results in energy compromise (12). Cell surface RTK's- PDGFR's are known sunitinib targets and inhibition of PDGFR's has been reported to play a protective role in hearts exposed to ischemic injury (22). However, PDGFR signaling functions were investigated by treating cardiac tissue or post-myocardial infarction tissue with exogenous PDGFR-  $\beta$ , the direct PDGFR's functions have not been elucidated. Chintalgattu et al (23) selectively blocked PDGFR-  $\beta$  in mice hearts and reported that in PDGFR-  $\beta$  mutant mice, cardiac function was compromised and angiogenesis was impaired. These results demonstrated that PDGFR-  $\beta$  is required to maintain cardiac function in response to mechanical stress and also for stress-induced cardiac angiogenesis. PDGFR-  $\beta$  regulates the heart and plays a positive role in maintenance. It is also required for angiogenesis and preservation of cardiac function in the presence of stress overload (23). This may be an off-target effect of sunitinib.

Arterial hypertension is another cardiovascular toxicity associated with the administration of sunitinib. The incidence of this adverse event is 17-43%. Of note, hypertension was found to be a biomarker of efficacy in patients with with metastatic renal cell carcinoma (mRCC) treated with sunitinib. Patients with mRCC and sunitinib-induced hypertension had better outcomes compared with those without treatment-induced

hypertension (24). The mechanism underlying the development of HTN has not been fully explained.

### Assessment of cardiotoxicity

Identification of patients with increased risk of cardiotoxicity consists of a careful baseline assessment of cardiovascular risk factors (**Table 1**), clinical history and examination, measurement of cardiac function. Cardiac biomarkers (natriuretic peptides or cardiac troponins) evaluation may be considered in addition. It is important to identify subclinical cardiac disturbance, which can have influence for decisions of choosing targeted therapy agent and setting indication for cardioprotective agents (25,26 ).

<b>Table 1. Factors associated with increased risk of cardiotoxicity</b>	
<b>Agent</b>	<b>Risk factors</b>
<b>Anti-HER2 compounds</b>	
<b>Antibodies:</b> Trastuzumab Pertuzumab T-DM1 <b>TKI:</b> Lapatinib	<ul style="list-style-type: none"> <li>• Previous or concomitant anthracycline treatment (short time between anthracycline and anti-HER2 treatment)</li> <li>• Age ( &gt; 65 years)</li> <li>• High BMI &gt;30 kg/mg2</li> <li>• Previous LV dysfunction</li> <li>• Arterial hypertension</li> <li>• Previous radiation therapy</li> </ul>
<b>VEGF inhibitors</b>	
<b>Antibodies:</b> Bevacizumab Ramucirumb	<ul style="list-style-type: none"> <li>• Pre-existing HF</li> <li>• Significant CAD or left side VHD (e.g. mitral regurgitation)</li> <li>• Chronic ischemic cardiomyopathy</li> <li>• Previous anthracycline usage</li> </ul>

<b>TKI:</b>	<ul style="list-style-type: none"> <li>• Arterial hypertension</li> <li>• Pre-existing cardiac disease</li> </ul>
Sunitinib	
Pazopanib	
Axitinib	
Neratinib	
Afatinib	
Sorafenib	
Dasatini	

### Diagnostic cardiac imaging methods

Echocardiography is suitable tool for the detection of myocardial dysfunction before, during and after cancer therapy (27, 28). Cardiac dysfunction related to targeted therapy is defined as a decreased in the left ventricular ejection fraction (LVEF) of 10% points, to a value below the lower limit of normal (27, 29). This decrease should be confirmed by repeated cardiac imaging done 2–3 weeks after the baseline diagnostic study showing the initial decrease in LVEF. Evaluation of LV function using multigated radionuclide angiography has been used for years to diagnose targeted therapy - induced cardiotoxicity with good accuracy and reproducibility. Cardiac magnetic resonance (CMR) is a helpful test for the evaluation of cardiac structure and function. It is useful to determine the cause of LV dysfunction and to clarify left and right ventricular function. Late gadolinium imaging may be useful to detect scarring or fibrosis, which may have prognostic implications in the context of impaired LV function (30, 31).

### Coronary artery disease (CAD)

Myocardial ischemia and ischemia-induced arrhythmias are side effects of several cancer agents. A recent meta-analysis on the risk of arterial thrombosis induced by anti-VEGF small molecule TKI's found an overall incidence of 1,7 % for sorafenib and 1,4 % for sunitinib (32). Sorafenib has also been reported to induce vasospasm (33). The diagnostic algorithm's used to

identify CAD in patients with cancer are the same as in patients without cancer, also echocardiography should be included as part of the diagnostic tool in these patients.

### Valvular heart disease (VHD)

Chemotherapeutic agents do not directly affect cardiac valves, but VHD may be observed in patients with cancer for several reasons, including pre-existing valve lesions, radiotherapy, infective endocarditis and secondary LV dysfunction. Echocardiography is recommended at baseline assessment and repeated echocardiography after targeted therapy in patients with cancer for the diagnosis and follow-up of VHD. CMR and computed tomography (CT) may be used to assess the severity of VHD, but cardiac CT is mainly useful for detecting extensive calcifications. Cardiac surgery is challenging in such patients because of mediastinal fibrosis, impaired wound healing and affected coronary artery, myocardial and pericardial disease. Transcatheter valve implantation may be an option in this situation (34).

### Arrhythmias

Arrhythmias can be present at baseline in 16–36% of treated patients with cancer. TKI's can cause atrial fibrillation, therefore electrocardiography and electrolyte monitoring during treatment should be considered at baseline, 7–15 days after initiation or changes in dose, monthly during the first 3 months and then periodically during treatment depending on patient status and the targeted therapy agent. Management generally relies on correcting the predisposing factors (e.g. concomitant electrolyte abnormalities, QT-prolonging drugs) (35).

### Arterial hypertension

Hypertension is a frequently found in oncologic patients. TKI's can cause new hypertension or destabilize

previously controlled hypertension, including severe hypertension (36, 37). The incidence and severity depends upon patient age, history of hypertension, type of cancer (i.e. renal vs. non-renal cell cancer), drug type and dose, schedule used and associated cancer therapies. Nitric oxide pathway inhibition, vascular rarefaction (i.e. reduced number of vessels), oxidative stress and glomerular injury are main action mechanisms. Drug-related hypertension can occur from initiation until 1 year after treatment onset in the case of sunitinib, but there is no evidence that antihypertensive therapy impairs oncology responses (38). Evaluation and management of arterial hypertension should be performed before initiation of a TKI's. Other medications used in these patients (e.g. steroids, non-steroidal anti-inflammatory drugs, erythropoietin) may also predispose to or cause hypertension. Angiotensin-converting-enzyme inhibitors (ACE inhibitors), angiotensin II receptor blockers (ARB) and non-dihydropyridine calcium channel blockers (amlodipine) are proposed as first-line therapies. ACE inhibitors and beta-blockers are the preferred antihypertensive drugs in patients with heart failure (HF) or at risk of HF or left ventricular dysfunction (39).

#### ***Peripheral vascular disease***

Severe peripheral artery disease (PAD) in the lower extremities can occur in patients treated with nilotinib, ponatinib used for chronic myeloid leukemia even when there is no cardiovascular disease risk factors. PAD can manifest in the first months of therapy or as a late effect several years after treatment. The assessment of PAD risk at baseline of treatment (risk factor assessment, clinical examination, ankle-brachial index measurement) is recommended. Asymptomatic or with intermittent claudication patient require risk factor control and periodic clinical, metabolic and hemodynamic supervision. Antiplatelet drugs should be considered mostly in symptomatic PAD. In case of

severe PAD at baseline or during cancer therapy, revascularization should be individualized and discussed in a multidisciplinary meeting with experts in hematology, vascular surgery and cardio-oncology.

#### ***Pulmonary hypertension***

The TKI imatinib improves hemodynamics in patients with advanced pulmonary arterial hypertension (PAH) (204,205). However, a drug of the same TKI family - dasatinib, used as second-line treatment for chronic myelogenous leukemia can induce severe precapillary pulmonary hypertension (40). This condition appears 8–40 months after exposure to dasatinib with clinical and hemodynamic presentation suggestive of PAH. Unlike other forms of PAH, this is often reversible after drug discontinuation or replacement with another TKI, such as nilotinib.

#### ***Myocardial dysfunction and heart failure***

Patients who have asymptomatic left ventricle dysfunction or HF during cancer therapy are likely to profit from ACE inhibitors or ARB's and beta-blocker treatment similar to the general HF population. Careful assessment of cardiovascular risk factors at baseline, close blood pressure monitoring and discontinuation of drugs known to raise blood pressure are essential to ensure effective management of heart function in patients treated with TKI's. Periodic screening with cardiac imaging and biomarkers, such as brain natriuretic peptide (BNP) should be considered, particularly in those treated with high cumulative doses or who demonstrated reversible LV dysfunction during cancer treatment (41).

#### **Conclusions**

As the application of targeted therapy in treatment of cancer is on the increases, extensive

research is required to understand in detail the mechanisms underlying the development of cardiovascular toxicities and promote the design of optimal drugs. Targeted cancer therapy is associated with fewer severe adverse effects comparing to chemotherapy. However, cardiotoxicity induced by TKI is common in clinical practice. New imaging technologies, such as three - dimensional

echocardiography and speckle tracking imaging may be used as surveillance of patients who are predisposed to cardiac dysfunction. It is essential to identify TKI induced cardiotoxicity and start treatment as early as possible in order to ensure not only optimal treatment of cancer but also patients prognosis and quality of life.

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