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REVIEW PAPER

Cardiotoxicity associated with tyrosine kinase-targeted anticancer therapy

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Abstract

Purpose of review: Tyrosine kinase inhibitors (TKIs) have shown clear survival benefits as effective targeted therapies in various hematological and solid malignancies. Important evidence, however, has shown that TKIs may lead to adverse effects such as cardiovascular toxicities, via off-target as well as on-target mechanisms. This review presents an overview of TKI-induced cardiotoxicity mechanisms, clinical manifestations, diagnosis, monitoring, and management options. Furthermore, we discuss current preclinical efforts and future investigations into alternative therapeutics for minimizing the cardiotoxicities associated with tyrosine kinase-targeted therapies.

Recent findings: Accompanying with the significant improvements toward targeted anticancer treatment, cardiotoxicity-related adverse effects are increasingly reported and have become an important public health issue. The TKI-induced cardiovascular toxicities include myocardial ischemia, heart failure, QT prolongation, and hypertension. Thus, the early awareness of cardiotoxicities, initiation of appropriate management, and close follow-up, may enhance the benefits of TKI therapy.

Keywords: Neoplasm, Drug therapy, Cardiotoxicity, Heart failure

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Introduction

Cancer and cardiovascular disease are the two leading causes of death in the world[1]. Recently, targeted therapies have become a powerful tool in cancer management, with significant survival benefits[2]. The development of tyrosine kinase inhibitors (TKIs) has provided a great step forward in targeted cancer treatments[3]. More than 30 TKIs are currently in clinical use or undergoing advanced clinical trials[4-8]. Tyrosine kinases (TKs) are enzymes that activate proteins by transferring a phosphate group to the tyrosine residues of proteins in signal transduction cascade. TKIs are highly selective for inhibiting tyrosine phosphorylation and do not inhibit protein kinases that phosphorylate serine or threonine residues[4].

There are two main drug classes of targeted cancer therapies: TK monoclonal antibodies (rituximab, alemtuzumab, trastuzumab, etc.) and small molecule TKIs (sorafenib, sunitinib, dasatinib, imatinib, nilotinib, etc.) (Table 1). TKIs were expected to be less toxic than conventional anticancer drugs, as they target the specific proteins involved in cancer cell proliferation. However, their widespread use has raised concern regarding cardiotoxicity and off-target effects[9]. The spectrum of cardiovascular toxicities associated with TKIs includes heart failure (HF), arrhythmia/QT prolongation, hypertension, and acute coronary syndrome (ACS)/myocardial ischemia. The risk of cardiac damage is higher in patients with a prior history of cardiac disease[4].

Currently, there is no clear consensus on the definition of cardiotoxicity. The Cardiac Review and Evaluation Committee of Trastuzumab-associated Cardiotoxicity defines cardiotoxicity as a decline of the left ventricular ejection fraction (LVEF), HF symptoms, an asymptomatic reduction of LVEF $\geq$10 to $<$55% or a symptomatic fall in LVEF $\geq$5 to $<$55%[10,11]. The US

Table 1. Classification of tyrosine kinase-targeted anticancer agents

Targets	VEGFR		ERBB/HER		BCR-abl PDGFR
Classes	Monoclonal antibody	Small molecule TKI	Monoclonal antibody	Small molecule TKI	Small molecule TKI
Agents	Ramucizumab	Sunitinib	ERBB1 (HER1)		Imatinib
	Bevacizumab	Neratinib	Cetuximab	Lapatinib	Dasatinib
		Pazopanib	Panitumumab	Erlotinib	Nilotinib
		Sorafenib		Gefitinib	
		Axitinib	ERBB2 (HER2)		
		Afatinib	Pertuzumab	Lapatinib	
		Regorafenib	Trastuzumab		

VEGFR: vascular endothelial growth factor receptor, ERBB: erythroblastic leukemia viral oncogene B, ERBB1 (HER1): human epidermal growth factor receptor, ERRB2 (HER2), BCR-abl: fusion protein encoded by the Philadelphia chromosome, PDGFR: platelet derived growth factor receptor, TKI: tyrosine kinase inhibitor.

Food and Drug Administration (USFDA) defines LVEF is a 40-49% with a $\geq$10% absolute decrease below baseline or a $<$40-45% drop with receptor tyrosine-protein kinase ERBB2 (also known as HER2) as being necessary to be monitored[10]. The American Society of Echocardiography and European Association of Cardiovascular Imaging define cardiotoxicity as global longitudinal strain (GLS) with a 10-15% early reduction[10]. Cardiotoxicities may be categorized as acute and chronic and can be classified into type I (early onset) and type II (late onset)[4]. Type I refers to irreversible cardiomyocyte (CM) injury, which is usually caused by anthracyclines and conventional chemotherapeutics, while type II is typically caused by novel biological-targeted inhibitors or antibodies[12].

This review describes the underlying mechanisms of the cardiotoxicities associated with TKI treatment and discusses current trends and importance of preclinical studies for assessing cardiotoxicity. We also present diagnostic tools, monitoring methods, and management options that are available in clinical practice for targeted anticancer therapeutics.

Mechanisms of targeted therapy-induced cardiotoxicity

TK inhibition has been described to cause cardiotoxicity by several different mechanisms (Figure 1). One of the most eminently evaluated targeted therapies is inhibitors of the vascular endothelial growth factor (VEGF) signaling cascade. VEGF induces angiogenesis through binding the VEGF receptor (VEGFR). The inhibition of angiogenesis stops growing tumors from seizing the body's natural processes[10,13]. Another popular target for cancer treatment is the erythroblastic leukemia viral oncogene B (ERBB), commonly referred to as HER. Normally, ERBB facilitates the proliferation, growth, and repairing of abnormal cells within the body. However, similar to the VEGF signaling pathway, oncogenic mutations in ERBB dominate cellular processes and encourage cancer cell proliferation[14]. TKI- and anti-VEGF-induced cardiotoxicity can occur through both on-target and off-target mechanisms. On-target cardiotoxicity takes place through drug interactions with the intended target kinases and homologous kinases CMs[15]. A representative drug that causes off-target cardiotoxicity is sunitinib[16].

Cardiotoxicity from VEGF-targeted therapy

VEGFR is one of the most important receptor tyrosine kinases (RTKs). The VEGF family is composes of seven members–VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, VEGF-F, and placental growth factor. VEGF-A is the most typical component, and the mRNA of VEGF-A is expressed in various tissues of the body, such as the lungs, heart, and kidneys[10,13]. Consequently, the VEGF signaling pathway plays a critical role in multiple signaling pathways that affect vasculature, and alterations to the VEGF pathway have been shown to have deleterious effects[17].

VEGF binds to three different receptors–VEGFR-1 (Flt-1), VEGFR-2 (Flk-1), and VEGFR-3[18]. The binding of VEGF to VEGFR-2 launches a tyrosine signaling cascade, which expedites cell growth, proliferation, migration, and vasodilation, all of which are important for angiogenesis[19]. Historically, the VEGF pathway can be targeted using several different methods, including recombinant receptors, monoclonal antibodies, or inhibitors of downstream kinase expression (TK inhibition) and signaling pathways[20].

Current anti-angiogenesis therapies, including VEGF inhibitors, have been shown to have adverse effects on the cardiovascular system[10,13,21,22]. Anti-VEGF therapies, such as specific VEGF antibodies and VEGFR TKIs, exacerbate left ventricular (LV) dysfunction, hypertension, QT interval prolongation, ischemic events,

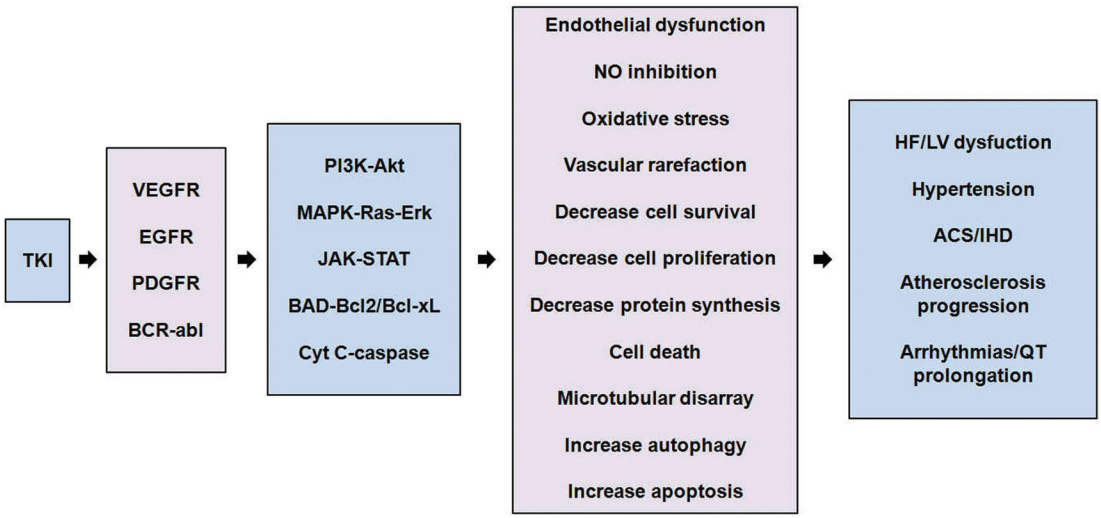

Figure 1. Mechanism of cardiotoxicity from tyrosine kinase-targeted therapy. Tyrosine kinase inhibitors bind their receptors extracellularly or intracellularly. Agent binding induces the initiation of various cellular signaling pathways. These processes are ultimately manifested as cardiovascular toxicities including heart failure, hypertension, myocardial ischemia, and arrhythmias. TKI: tyrosine kinase inhibitor, VEGFR: vascular endothelial growth factor receptor, EGFR: epidermal growth factor receptor (also known as ERBB1 or HER1), PDGFR: platelet derived growth factor receptor, BCR-abl: fusion protein encoded by the Philadelphia chromosome, PI3K: phosphatidylinositol 3-kinase, Akt: protein kinase B, MAPK: mitogen-activated protein kinase, Ras: rat sarcoma virus oncogene, Erk: extracellular signal-regulated kinase, JAK: Janus kinase, STAT: signal transducer and activator of transcription protein, BAD: Bcl-2–antagonist of cell death, Bcl: B-cell lymphoma, Bcl-xL: B-cell lymphoma-extra large, Cyt: cytochrome, NO: nitric oxide, HF: heart failure, LV: left ventricle, ACS: acute coronary syndrome, IHD: ischemic heart disease.

thromboembolic events, the rapid acceleration of atherosclerosis, and cardiovascular disease and even cause death[23]. The most common cardiovascular adverse effect associated with these drugs is hypertension, due to increased endothelin-1 production, decreased nitric oxide production, and capillary rarefaction in the endothelium[7]. Coronary microvascular dysfunction caused by the loss of vascular pericytes has been described in in vivo studies of sunitinib[4,8]. In terms of LV dysfunction, the molecular mechanisms of cardiotoxicity caused by TKIs remain poorly understood. The suggested mechanisms of sunitinib- and sorafenib-induced cardiotoxicity include the following[24]: inhibition of platelet-derived growth factor receptor (PDGFR) signaling, inhibition of angiogenic growth factors, inhibition of c-Kit signaling, impaired prosurvival signaling, alterations in AMP-activated protein kinase (AMPK) activity that result in mitochondrial dysfunction, and energy compromise.

Cardiotoxicities from ERBB1 (HER1)- and ERBB2 (HER2)-targeted therapies

Anticancer therapies that target the ERBB family of TKs have been successfully used in the treatment lung and breast cancer subtypes[25,26] cancer. These inhibitors are being increasingly studied in a variety of malignancies, including gliomas[27] and prostate[28], ovarian[29], colorectal[30], pancreatic[31], and head and neck[32] cancers. However, the ERBB pathways that are inhibited by anticancer therapies also play roles in the maintenance of cardiac homeostasis, and their inhibition can have important cardiovascular adverse effects, which most remarkably have led to LV systolic dysfunction and overt HF[25].

The ERBB family consists of four membrane-bound protein TKs that are often mentioned under different names that reflect their distinct receptor functions and paths of discovery[25]. The ERBB family of RTKs includes ERBB1 to 4, which share a common transmembrane RTK structure that includes an extracellular region, a single transmembrane-spanning region, and a cytoplasmic TK domain[25]. Each ERBB RTK has specific ligand binding characteristics that cause receptor hetero- or homo-dimerization, and the activation of intrinsic TK domains results in phosphorylation of specific TKs within the cytoplasmic domain[25]. There are three main pathways that can be induced upon the activation of ERBBs: the phosphatidylinositol 3-kinase (PI3K)–protein kinase B (Akt) pathway, the mitogen-activated protein kinase (MAPK)–rat sarcoma virus oncogene (Ras)–extracellular signal-regulated kinase (ERK) pathway, and the Janus kinase–signal transducer and activator of transcription protein (STAT) pathway,

which are all responsible for the regulation of the cellular growth, metabolism, and survival[33-36].

Cancer therapeutics that target ERBBs predominantly use two strategies: humanized monoclonal antibodies against the extracellular receptor domains or administration of small molecule TKIs, which can target both receptor and non-receptor TKs[25]. Antibody binding leads to receptor internalization, prevents activation of the downstream signaling pathways, and decreases receptor expression on the cell surface[25]. Small molecule TKIs function as ATP analogues and inhibit downstream intracellular signaling by blocking ATP binding sites on the catalytic domain of the receptor TK[37]. Importantly, the interruption ERBB receptor downstream signaling releases cytochrome C (Cyt C) from the mitochondria and reverses Bcl-2–antagonist of cell death (BAD) inhibition, which suppresses antiapoptotic B-cell lymphoma-extra large (Bcl-xL) expression, induces caspase activation, and leads to cell death[25].

Cardiotoxicity from other receptor TKIs

Several TKIs including dasatinib, imatinib, and nilotinib target the BCR-Abl kinase and the PDGFR, which TK targets in chronic myelogenous leukemia. These agents have been reported to cause thromboembolism and pulmonary hypertension[4].

Clinical manifestations of TKI-induced cardiotoxicity

Clinical manifestations of cardiotoxicity from TKIs have various features that are due to several different mechanisms.

Hypertension

TKIs that disturb the VEGF signaling pathway have been reported to elevate blood pressure[38]. The frequency of such adverse events varies between 11% and 45%, in patients treated with VEGFR inhibitors[9]. Hypertension incidences have been estimated to range from 17-42% with sorafenib and 15-47% with sunitinib[7,39,40]. The onset of TKI-related hypertension is variable and can occur 1 year after treatment or within 24 hours. The available data demonstrate that the risk of hypertension substantially depends on tumor type. The risk of developing hypertension is significantly higher in patients with renal cell carcinoma (RCC) than those with non-RCC tumors[41].

Heart failure and LV dysfunction

According to the European Society of Cardiology (ESC) Position Paper[9], LV dysfunction occurs most frequently with the use of sorafenib (4-8%), sunitinib (2.7-19%), and pazopanib (7-11%), and less frequently with lapatinib (0.2-1.5%) and imatinib (0.2-2.7%).

Acute coronary syndrome/Myocardial ischemia

TKIs exert a wide range of adverse effects on coronary vessels, including vasospasm (sorafenib, nilotinib), direct antiangiogenic and proatherogenic effects on endothelial cells (nilotinib, ponatinib), procoagulant effects (sorafenib, sunitinib, nilotinib), and acceleration of atherosclerotic processes (sorafenib, nilotinib). The risk of arterial thrombosis has been estimated to be 1.4% for sunitinib and 1.7% for sorafenib[9,42].

Arrhythmia/QT prolongation

A variety of arrhythmias can develop after TK-targeted anticancer therapy. One severe form is ventricular arrhythmia (torsade de pointes), which results from the prolongation of the QT interval. These arrhythmias may be due to indirect influences, through ACS/ischemia, or direct TKI electrophysiological effects on CMs or LV dysfunction. A significant QT-prolongation has been described for sunitinib, vemurafenib, sorafenib, cabozantinib, nilotinib, and vandetanib[9,43].

Monitoring and treatment of TKI-induced cardiotoxicity

Cardiac monitoring prior to and during anticancer treatment mainly focuses on several biomarkers and cardiac imaging modalities, such as echocardiography, cardiac magnetic resonance imaging (MRI), and nuclear multiple gated acquisition scans, to assess changes in cardiac function[25].

Biomarkers play crucial roles in the early detection of cardiotoxicity. The abnormal or elevated expression levels of several biomarkers can be used as indicators for evaluating and screening risk factors for future cardiotoxicities. Interleukin-6 (IL-6) leads to inflammation and increases blood pressure. The overexpression of IL-6 plays a role in drug resistance, inhibits cell apoptosis, and promotes angiogenesis[10,44]. Increases in brain-type natriuretic peptide (BNP), N-terminal-pro-BNP, and troponin (Tn)-I have all been linked to drops in LVEF[4,10,45]. Plasma myeloperoxidase levels are also predictive of decreased myocardial function[22]. Innovative imaging parameters have been explored to detect early markers of myocardial injury that occur before definite changes in LVEF are observed. Myocardial strain or GLS assessments, using speckle tracking echocardiography, have become the most hopeful predictors of future LVEF decline[25]. Cardiac MRI has re-

cently emerged and is used as a gold standard imaging technique. It is accurate, reliable, reproducible, and has higher sensitivity than 2D- or 3D-echocardiography in identifying early changes in regional and global LV function, and its high contrast-to-noise ratio presents outstanding structural characteristics[46,47]. Current recommendations for LV assessment after ERBB2-targeting trastuzumab treatment are as follows: serial echocardiograms at baseline and every three months are recommended during trastuzumab therapy. If LVEF decreases >16 points or 10-15 points from baseline to below the lower normal limit, hold trastuzumab for four weeks and perform cardiology consultation. If LVEF remains reduced or if any symptoms of HF are observed, consider the permanent discontinuation of trastuzumab treatment[25].

Providentially, most patients with ERBB-targeted drug-associated cardiotoxicities recover cardiac function after early cardiotoxicity identification, appropriate monitoring, and management[48,49]. In addition to temporarily discontinuing ERBB-targeted therapy, standard HF managements, including renin-angiotensin-aldosterone system antagonists and β-adrenergic blocking agents, are the main therapeutic strategies[25,50].

Preclinical investigations of cardiotoxicities related to TKIs

As above described, some TKIs are associated with severe cardiotoxicities. Given these life-threatening complications, cardiovascular safety has been recognized as a challenging aspect for basic researchers, drug developers, clinicians, and regulators, all of whom are investigating strategies to predict, detect, and prevent drug-associated cardiotoxicity[1,5,51]. However, preclinical platforms for assessing drug-induced cardiotoxicity use animal models, which inaccurately predict human cardiac pathophysiology because of interspecies differences in cardiac electrophysiology, structure, and genetics[3,52]. Therefore, new approaches are needed to estimate the cardiotoxicity of anticancer drugs. Over the last 10 years, published preclinical studies have revealed that TKIs lead to cardiotoxicity in isolated perfused hearts, human-induced pluripotent stem cell-derived CMs (hiPSC-CMs), and tissue-engineered heart tissue (TEHT), all of which predict a drug's potential for cardiac toxicity relatively well[1].

Previously, an isolated retrograde perfused rat heart model was used to evaluate changes in LV function, as assessed by LV pressure parameters, flow rates, heart rate, and protein biomarkers that included tumor necrosis factor-alpha, BNP, IL-6, and cardiac Tn-T and Tn-I[53]. HiPSC-CMs recapitulate many of the physiological characteristics of adult human CMs and are of growing interest as in vitro models for identifying drug toxicities and responses, determining potential drug targets, and understanding the mechanisms underlying genetic disease. Furthermore, they may predict relevant human effects more inexpensively and accurately than other cell or animal models[54]. TEHT is an in vitro force-producing, 3D cardiac tissue model with high levels of reproducibility. This system is composed of a dissociated fibrin matrix and CMs, between flexible silicone posts[55]. A recent study demonstrated the effects of nine small-molecule TKIs on TEHTs from neonatal rat CMs by analyzing histologies, contractile functions, organelle ultrastructures, and creatine kinase and lactate dehydrogenase activities[56].

With this information, regulatory agencies and drug developers are now able to better evaluate TKI-induced cardiotoxicities. As a result, since 2013, more TKIs have been approved and certified, and those with various TKI-induced cardiotoxicities in preclinical studies have been submitted for regulatory review[1]. Choosing the appropriate preclinical investigation parameters is the key to carrying out a successful study. Thus, designing and applying a stringent preclinical platform, both in vivo and in vitro, is necessary for assessing a new drug's cardiotoxic potential[1].

Conclusion & Future directions

Research into molecular pathways of ERBB signaling and the discovery of ERBB2/HER2 therapy-related cardiac dysfunction has revealed a new role of neuregulin (NRG) in cardiac homeostasis. NRG is a peptide growth factor that binds and activates ERBB2/ERBB4 and ERBB4/ERBB4 heterodimers and homodimers, causing the activation of downstream kinases[25]. During embryogenesis, NRG signaling regulates the proliferation, growth, and differentiation of neonatal CMs, whereas in the adult heart, the NRG pathway is involved in preventing pathologic remodeling and maintaining the myocardial architecture[57,58]. The discovery of NRG as a stress-induced mediator of myocardial repair give rise to investigation into recombinant NRG-1β as a potential therapeutic candidate for systolic HF[59], thus providing an attractive example of distinct opportunities to identify new cardiovascular disease targets. NRG is also being explored as a biomarker in patients receiving ERBB2/HER2-targeted therapies and anthracyclines, as higher baseline NRG levels have been suggested to identify patients who are at higher risks for significant myocardial toxicities[60,61].

Cardiovascular toxicities from anticancer therapies should be minimized, if possible. The improved pre-

clinical screening of anticancer agents for minimal cardiac drawbacks will greatly benefit cancer therapies[1]. To access difficulties in drug development, the National Institutes of Health (NIH) recently funded efforts to reinvent 3D micro-fluidic organ systems ("tissue/organ-on-a-chip") using stem cell-derived human cells that represent the characteristics and function of at least 10 major organ systems[62]. The use of these human organ micro-systems, which remain viable in culture conditions for at least a month, can avoid species differences between humans and current animal models in identifying specific drug metabolizing enzymes and cellular responses. Such systems may be able to predict and screen for drugs that have anticancer efficacy, while minimizing myocardial toxicity, in the same in vitro platform[1].

The level of homology of intracellular mediators and receptors between normal and malignant cells can cause on-/off-target therapeutic toxicities. To develop drugs with little or no unwanted adverse effects on critical organs, such as the heart, other strategies may be needed, such as pharmacological distinction between myocardial and cancer targets or drugs with greater cancer-specific potencies that generate antitumor activities at concentrations far below those that induce cardiotoxicity[1]. For instance, the co-administration of apoptosis/necrosis inhibitors or autophagy inducers[63], which target unique proteins specific to the cardiotoxicity pathways of chemotherapeutic drugs, is one such promising approach. This will help overcome cardiotoxicities, without compromising the antitumor activity of the drugs that are intended to treat a certain cancer[3]. Another promising strategy is the activation of compensatory signaling pathways. For example, VEGFR2/PDGFR-inhibiting TKIs can augment a survival of CM and rescue cardiotoxicity by activating compensatory prosurvival insulin/insulin-like growth factor-1 signaling pathways[64]. In future, more efforts and studies towards identifying different proteomic or genetic differences between cancer and healthy tissues may facilitate the development of anticancer agents with low or no cardiotoxicity[1]. However, for the time being, we should keep in mind that TKIs cause cardiovascular toxicities, including heart failure, hypertension, QT prolongation, and myocardial ischemia. Therefore, early identification of crucial cardiotoxicities, regular monitoring, initiation of proper treatment, and close follow-up, will enhance the benefits of TK-targeted therapy.

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